

# **Spatial Epidemiology of Indicators of Male Reproductive Health in Scotland**

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# Abstract

## Background

In recent years there are a number of reports showing a deterioration in male reproductive health, i.e. diminished semen quality and increases in the incidence of testicular cancer and the congenital malformations cryptorchidism and hypospadias. It is hypothesised that these changes have been caused by increasing *in utero* exposure to environmental oestrogens and/or anti-androgens.

## Objectives

- (i) Describe the geographical distributions of three indicators of male reproductive health in Scotland (i.e. testicular cancer, cryptorchidism and hypospadias).
- (ii) Describe the conjoint geographical distribution of the three indicators specified in (i).
- (iii) Identify explanatory factors that might account for the geographical distribution of male reproductive health in Scotland.

## Methods

An epidemiology study modelling the geographical distributions using routinely collected data of the three indicators. The primary assessment of the geographical distribution of the indicators was by means of the relative risks at postcode sector level. If geographically varying risk factors (environmental or not) are associated with these conditions then would expect to see clustering of relative risks. Bayesian methods were used to estimate the relative risks so as to account for their variability due to areas with small number of cases. These Bayesian models were developed further by including potential covariates to assess if these area specific factors explain the spatial variation of the three indicators. In addition, Bayesian modelling of individual data pertaining to the cryptorchidism cases was also carried out to explore whether the spatial variation in risk might also be explained by the nature of the cases within each postcode sector rather than area specific covariates. Finally, a Bayesian model which combined all three indicators was developed to examine the spatial relationships between the three disease/conditions.



## Results

There are similarities in the spatial pattern of the cryptorchidism and hypospadias relative risks, with both conditions having clusters of high relative risks in the East and South-West of Scotland. The spatial variation of the testicular cancer relative risks is not similar to the other two conditions nor is it conclusive that it has a distinct spatial pattern. The relative risks of the postcode sectors for all the indicators are associated with radon measurements and the rural/urban indicator. The spatial analysis of individual information concerning the cryptorchidism cases indicate that the spatial variation of the relative risks might also be explained by individual information; namely maternal age and co-morbidity with hypospadias.

## Conclusions

There does appear to be geographically varying risk factors associated with these three conditions. Furthermore, as the spatial variation of cryptorchidism and hypospadias is similar it is likely that they have some common aetiology. As the same risk factors were found to be associated with testicular cancer and the congenital malformations, then this carcinoma appears to share some aetiology with cryptorchidism and hypospadias. Therefore there are geographically varying risk factors whose exposure occurs *in utero*, that are associated with all three conditions, providing some evidence to support the proposed hypothesis. However, the common aetiology of these conditions could not only be environmental but also due to genetic and life-style factors, that could pertain to the individual cases rather than the specific area. Therefore, further studies are required to investigate the associations between all the disease/conditions of male reproductive health and the various potential risk factors.

## **Declaration**

I, Tracey Farragher, declare that I have written the following thesis, that the work within it is my own and it has not been submitted for any other degree or professional qualification.

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## Chapter 1 : Introduction

Over recent decades, there have been growing concerns regarding men's reproductive health. These concerns stem from several reports in various countries showing that over time semen quality has declined, testicular cancer incidence has increased and the incidence of the congenital malformations cryptorchidism and hypospadias have risen.

It has been postulated that this reported decline in male reproductive health is a result of increasing exposure *in utero* to particular environmental chemicals, and that the various conditions associated with male reproductive health are varying degrees of one underlying entity - Testicular dysgenesis syndrome (TDS).

However, these statements as regards male reproductive health remain controversial. Firstly, the evidence that shows temporal or geographical differences is not robust for some of these conditions. Furthermore, other potential risk factors not related to the proposed *in utero* environmental exposure may also be involved in any proposed temporal and geographical differences in these conditions. Finally that evidence showing associations between these conditions is limited.

Chapter 2 outlines these debates regarding male reproductive health. Firstly, the evidence used to argue that there has been a decline in male reproductive health and that these changes are due to a common environmental aetiology is reviewed for each disease/condition. Secondly, the proposed TDS hypothesis is discussed in terms of the known aetiology and biology of the conditions.

The review of the evidence used to show a decline in male reproductive health highlights that there are concerns about the robustness of this research for certain conditions. Therefore doubts remain that there are either temporal or geographical differences for some of these conditions. If the differences in conditions over space and time could be due to differences in data quality then the basis for the proposed changes in *in utero* environmental exposure is undermined. Furthermore, the examination of the current literature shows the complex nature of the known aetiology of all of these conditions. Subsequently, the testicular dysgenesis syndrome hypothesis might not be the only possible explanation for the proposed decline in

these conditions and that other non *in utero* environmental risk factors might be involved.

Therefore, there would appear to be a number of unresolved issues from previous male reproductive health research, which this research project aims to address. The aims of the research project are to:

- (i) Describe the geographical distributions of three indicators of male reproductive health in Scotland (i.e. testicular cancer, cryptorchidism and hypospadias).
- (ii) Describe the conjoint geographical distribution of the three indicators specified in (i).
- (iii) Identify explanatory factors that might account for the geographical distribution of male reproductive health in Scotland.

The use of consistently collected high-quality data in this analysis would overcome concerns of some of the previous research on these conditions. Furthermore, a combined analysis of these conditions, would take into account all aspects of the proposed syndrome TDS, rather than focusing on one condition and so explore possible relationships. Finally, the exploration of potential risk factors would take into account that more than one risk factor could be involved and that they could be involved in all the conditions aetiology or specific ones.

Chapter 3 outlines the methods used to achieve these aims, i.e. the data used and the analysis carried out. As the study is a spatial epidemiological analysis, this is a key theme of this chapter. The concepts of spatial epidemiology are introduced and the particular spatial analysis methods used are outlined. As the spatial analysis is based on Bayesian Methods, these too are introduced.

The next four chapters provide the results of the spatial analysis, the first three of which are disease-specific.

The cryptorchidism analysis (Chapter 4) shows that there is distinct pattern to the relative risks per postcode sector estimated from the Bayesian Hierarchical models. There are clusters of higher relative risks in the East and South-West and clusters of lower relative risks in the North and a corridor reaching from the central Borders to



the West Coast of Scotland. This spatial pattern of the cryptorchidism relative risks appeared to be explained by a rural/urban indicator (population density) and two radon measurements – mean radon level Bq/m<sup>3</sup> within each postcode area and the proportion of measurements within a postcode area that exceeds 200 Bq/m<sup>3</sup>. The spatial variation of cryptorchidism could also be explained by information concerning the cases themselves; namely maternal age and co-morbidity with hypospadias.

The spatial pattern of the hypospadias relative risks (Chapter 5) was very similar to those for cryptorchidism, suggesting a common aetiology. The spatial variation of hypospadias was also explained by the rural/urban indicator and one of the radon measurements namely, the proportion of measurements within a postcode area that exceeds 200 Bq/m<sup>3</sup>, but not the mean radon level. Again, suggesting some common aetiology.

The spatial pattern of the testicular cancer relative risk (Chapter 6) was not similar to the cryptorchidism or hypospadias cases. Furthermore, it is inconclusive that there was a distinct spatial pattern to the variation in relative risks. However there was some evidence that higher relative risks were clustered in the far North and South, with lower relative risks in a region from the Central Belt to the South West. Although the spatial variation of the testicular cancer relative risk was different from the cryptorchidism and hypospadias, it too was explained by the rural/urban indicator, and the mean radon level Bq/m<sup>3</sup> within each postcode area.

The final results chapter provides a combined analysis of the three disease/conditions (Chapter 7). This analysis confirms the similarities between the spatial patterns of cryptorchidism and hypospadias, and the dissimilarities between these two congenital malformations and testicular cancer.

The final chapter brings together the results raised from the analysis in context of the study aims and current male reproductive health research. From this analysis there appears to be geographically varying risk factors, whose exposure occurs *in utero*, that are associated with these three conditions. Furthermore, the analysis provides evidence of common aetiology particularly between cryptorchidism and hypospadias.

The exploration of possible aetiology shows that various risk factors are associated with these conditions and reflect that both environmental, genetic and life-style factors may explain the geographical differences. Further studies are required to explore the aetiologies of these conditions in order to answer this important health question, and a number of directions are suggested in the conclusion of the discussion chapter.

## Chapter 2 : Male Reproductive Health

### 2.1 Introduction

In recent years there has been accumulating evidence of a deterioration in male reproductive health, in terms of semen quality, testicular cancer and the congenital malformations cryptorchidism and hypospadias. It is hypothesised that these changes in male reproductive health are a result of increasing *in utero* exposure to environmental oestrogens and anti-androgens. However this hypothesis and some of the evidence that led to the concerns regarding male reproductive health are controversial.

This chapter reviews previous male reproductive health research and highlights remaining questions and uncertainties. The research presented here aims to examine the arguments and research put forward to suggest that male reproductive health is in decline, and the hypothesis postulated to explain these changes. Firstly, the evidence that has been used to show a decline in the indicators of male reproductive health, namely testicular cancer, cryptorchidism, hypospadias and semen quality is considered in terms of the known aetiology and morphology of each condition. Furthermore, the argument that these conditions have some common aetiology is also examined within the same context. Finally, the hypothesis known as Testicular Dysgenesis Syndrome (TDS), which is postulated to explain the adverse trends in male reproductive health, is then reviewed taking into consideration the previously outlined background of the various conditions.

Therefore this chapter describes the concerns in relation to male reproductive health and highlights the outstanding issues raised from the previous research. While not all these issues are addressed by this research project it is necessary to discuss them. As the research project carried out stems from the concerns in relation to male reproductive health and the proposed environmental aetiology, the previous research needs to be examined to place the project in context.



## 2.2 Evidence for a decline in male reproductive health

As will be shown in this section, the evidence of a temporal decline is not conclusive for all conditions related to male reproductive health. This is largely due to the quality of data previously used to show a decline in certain conditions and investigate their aetiology. Therefore, the proposed decline in male reproductive health could be based on limited evidence for particular conditions, and so any research into these conditions should aim to overcome the limitations of previous research. Furthermore, while there is some evidence of common aetiology for these conditions, other risk factors that are not relevant to the proposed *in utero* environmental exposure hypothesis also have important associations with the various conditions. Consequently, these other risk factors might in part explain variations in the conditions – either temporal or geographical, and so they should be considered when any research of these indicators is carried out.

Each of the conditions related to the decline in male reproductive health are discussed separately. The reports of a temporal decline in each condition are discussed in relation to the known aetiology of each. The morphology of each of the conditions is outlined first so as to provide the necessary background required to review and so understand their aetiology and epidemiology.

Although this research project is a geographical based one, as can be seen this is not the emphasis of the literature reviewed here. The temporal changes in the various conditions are examined in detail as these reports instigated the concerns in relation to male reproductive health. Also, the changes over time in the conditions were used as evidence to argue an environmental cause to the decline in male reproductive health. Furthermore, little geographical analysis has been carried out on these conditions, even though there is a proposed environmental aetiology. However, where geographical analysis has been done on certain conditions, it is discussed.

## **2.2.1 Testicular Cancer**

While testicular cancer represents only 1% of cancers in men overall, it is the most common malignancy in men aged 15 to 35 (Bringhurst and Amato, 2002). Furthermore, there is considerable evidence that the incidence of testicular cancer has risen over the last 60 years in Western Europe, Japan and the USA (Irvine, 2001). This section will review the current literature concerning testicular cancer in relation to these two statements. Firstly, the morphology, natural history, treatment and prognosis will be outlined to provide an overview of the disease. Secondly a review of the known epidemiology and aetiology of testicular cancer will highlight the disease's place in the current concerns regarding male reproductive health.

### **2.2.1.1 Morphology of testicular cancer**

As outlined in a review of its oncology, testicular cancer is a general term for several distinct but related neoplasms (Bringhurst and Amato, 2002). The neoplasms are distinct in their incidence (age and rates) and prognosis as well as their pathology, although there are overlaps between them. According to the oncology review, an epidemiology review of the disease (Buetow, 1995) and a summary of its pathology (Robbins *et al.*, 1999), there are several methods of morphology classification used across the world. Furthermore there are a large number of morphological types of testicular cancer within each of the classifications used. This has resulted in confusion and difficulties in comparing across classifications of neoplasms. However, these reviews suggest that the main differentiation between the neoplasms is whether they are germ-cell or non germ-cell. As noted in the oncological review, the majority (93%) of primary testicular cancer cases are germ-cell neoplasms (Bringhurst and Amato, 2002). As the non germ-cell neoplasms are of low prevalence, the sub-categories of these neoplasms are not detailed here.

Within the germ-cell neoplasms classification there are two groups of malignancies, the seminomas group and the nonseminomatous tumour group (NSGCT). These are different from a clinical standpoint both in terms of treatment and prognosis and also prevalence. While within each group of tumours there are further sub-classifications with differing pathology, the main differences are between the two germ-cell groups. For instance, while the tumours within the categories in the NSGCTs group are



diverse, they frequently present together. In general, the NSGCTs present in specific age groups while seminomas present at a broad age range and are generally slower to spread and less aggressive than the NSGCTs.

In the germ-cell neoplasm group there is also a non-malignant germ cells known as carcinoma-in-situ (CIS). These cells are known as precursors to testicular cancer, for example, a study found that 7 years from incidence of CIS, 70% of cases have progressed to malignancy and none had regressed (Skakkebaek, Berthelsen, and Muller, 1982). Furthermore, between 75% and 99% of testicular cancer tumours are found with CIS adjacent to them (Gondos, Berthelsen, and Skakkebaek, 1983). As will be seen in the overview of the disease's epidemiology, the aetiology of these non-malignant cells could give an insight into the aetiology of testicular cancer.

The different classifications for testicular cancer have different methods of diagnosis and treatment. While the diagnosis and treatments methods, are dependent on the morphology category of testicular cancer, generally for all cases the prognosis of the disease is good. A study of trends in testicular cancer cases in England and Wales between 1971 and 1999 found that the age-standardised mortality rate decreased by 71%; from 1.0 per 100,000 to 0.3 per 100,000 (Power *et al.*, 2001). The increase in survival rate has led to the misperception that the increase in incidence of testicular cancer is as a result of better diagnosis and treatment. However, as noted by Sharpe, while treatment has improved the diagnosis of testicular cancer has been consistently accurate (Sharpe, 2002). Therefore the increase in incidence outlined next is due to reasons other than better diagnosis.

#### **2.2.1.2 Epidemiology and aetiology of testicular cancer**

Many studies have found increases in the incidence of testicular cancer in developed countries. The study of trends in testicular cancer cases in England and Wales between 1971 and 1999, mentioned previously in relation to survival, also found an 88% increase in the age standardised incidence rates; from 2.9 per 100,000 in 1971 to 5.4 per 100,000 in 1997 (Power *et al.*, 2001). Adami *et al.* compared the incidence of testicular cancer in nine Northern European countries from as far back as 1943 through to 1989 (Adami *et al.*, 1994). They observed increases in the age-standardised incidence rates in all the countries; between 2.3 to 3.4 per cent annually



in the Nordic countries and by about 5 per cent in Poland and Germany. Another comparison in Europe, this time of six countries, again found increases in testicular cancer incidence; ranging from 2.3% increase annually in Sweden to 5.2% annually in East Germany (Bergstrom *et al.*, 1996). According to data from the Surveillance, Epidemiology and End Results Programme (SEER), in the US, the incidence of testicular cancer has increased by 51% from 3.61 per 100,000 in 1973 to 5.44 per 100,000 in 1995, (McKiernan *et al.*, 1999).

While there is very strong evidence of an increase in incidence of testicular cancer across the developed world, there are a few exceptions to this trend. For example, the incidence in the African-American population has not risen over time and has remained at a low rate (Van Den Eeden and Weiss, 1989). Also, a high annual incidence of 10 per 100,000 has remained stable between 1974 and 1987 in the Canton Vaude, Switzerland (Levi, Te, and La Vecchia, 1990). Furthermore, studies that have shown an increase in incidence have also reported a stabilising of rates in the most recent years. For example, further analysis of the SEER data showed that the rates of incidence of testicular cancer levelled off in the early 1990's (Pharris-Ciurej, Cook, and Weiss, 1999). And while an analysis of the incidence trends of Denmark showed an increase of 2.6% per year from 1943 to 1996, it also suggested that the incidence rates stabilised for birth cohorts after 1963.

The testicular cancer registry data used in these studies have on the whole been consistently recorded and any changes in registration or diagnosis can explain little of the overall rise in incidence (Buetow, 1995). For example, the comparisons of European countries examined differences in ascertainment and found that even when these were accounted for, there still appeared to be changes in time and between countries (Adami *et al.* 1994; Bergstrom *et al.* 1996).

Therefore the evidence does indicate that there has been an increase in incidence of testicular cancer over time, and that geographical differences occur. These and other studies have been used to suggest that this is a result of increasing geographically varying environmental factors namely *in utero* exposure to environmental oestrogens and anti-androgens, in combination with a genetic predisposition. Furthermore, previous studies have been used to argue that environmental rather than genetic

factors are the most important. However separating out genetic and/or environmental factors' roles in the risk of testicular cancer is very difficult and might not be appropriate, as it could be an interaction between the two. Also, as will be seen it is far from clear that these are the only potential mechanisms to explain the increase in testicular cancer incidence.

Bergstrom *et al.*'s comparison of six European countries found that birth cohort was a stronger effect on testicular cancer risk than year of incidence. For example, men born in 1965 had a risk of developing testicular cancer that was 3.9 (Sweden) to 11.4 times (East Germany) higher than for men born in 1905. Other studies have also found that later year of birth is associated with increased testicular cancer risk (Toppari *et al.*, 1996;Zheng *et al.*, 1996). It is argued that the association between the increase in risk and when the man was born suggests that whatever is causing these changes only occurred in relatively recent years. Therefore it would suggest environmental factors rather than an accumulation of genetic defects are at play. However, the association between birth cohort and increasing risk are more likely to be a genetic/environmental interaction. In fact, 80% of germ cell tumours have found to have a chromosomal abnormality of the isochromosome i(12p).

There are studies that provide evidence that there is 'genetic pre-disposition' to testicular cancer. It has also been found that fathers of testis cancer sufferers have an increased risk (1.96; 95% CI: 1.01-3.43) of the disease, and that brothers of a subcohort of these men with testicular cancer have an even higher risk (RR = 12.3; 95% CI: 3.37-31.5) (Westergaard *et al.*, 1996). Furthermore, twins of brothers who have had testicular cancer have a 12 to 37 fold increased risk of testicular cancer (Swerdlow *et al.*, 1997). These studies support the possibility that genetic factors may be involved in the development of testicular cancer. However, they could also support the possibility of similar environmental conditions, particularly in siblings (Irvine, 1999).

The comparisons of country specific rates have been used to show a geographical variation of the incidence of testicular cancer. However, only one study appears to have looked at the spatial variation of testicular cancer at a small area level (Toledano *et al.*, 2001). This analysis looked at electoral ward variation in incidence



in two regions of Great Britain (North West Thames and Yorkshire) to represent a diverse mix of urban, suburban and rural populations. No local spatial variation in the incidence of testicular cancer was found. This could be because no spatially varying factor is associated with testicular cancer, but also because of the long latency periods between incidence and the possible exposure *in utero*, and the effects of migration. With a long latency period, the chance of an individual moving is increased, and this might be within, out or into the particular region studied. Therefore the spatial variation of the incidence of testicular cancer will reflect this migration rather than the geographical variation of the underlying potential exposure. This is particularly relevant to the regions studied as both include metropolitan areas so increasing the likelihood of migration. Furthermore, the age range of highest incidence of testicular cancer is the 20's and 30's which is when the highest rates of migration occur.

Other studies have found associations between testicular cancer and other indicators of male reproductive health which might indicate that they have a common aetiology. The strongest risk factor for testicular cancer found so far is cryptorchidism. One study in Denmark estimated that men with a history of cryptorchidism had a 3.6 fold (95% CI 1.8-6.9) increased risk of developing testicular cancer (Moller, Prener, and Skakkebaek, 1996) while another study also in Denmark found a 5.2 fold risk (95% CI 2.1-13.0) (Prener, Engholm, and Jensen, 1996). Perner and colleagues also found an association with other congenital malformations such as inguinal hernia, hypospadias and hydrocoele and the risk of testicular cancer. Other studies have found strong associations between testicular cancer risk and cryptorchidism in other settings (Forman *et al.*, 1994; Weir *et al.*, 2000).

While cryptorchidism has the strongest association with testicular cancer risk (Buetow, 1995), there are other possible reasons for this rather than just common aetiology. The continual higher local temperature could result in damage to the testes, and an undescended testis might be more likely to be abnormal than a partly or fully descended one. Both of these scenarios have the potential of resulting in neoplasms in the future, although there is conflicting evidence on which holds true. Furthermore, it is unclear if the potential damage to the testes is reversed by the



correction of cryptorchidism, irrespective of age (Buetow, 1995). Therefore, the association between testicular cancer and cryptorchidism could well be due to a common aetiology but other mechanisms could also explain the relationship.

It has been suggested that the geographical variation of testicular cancer might be linked to similar differences in semen quality so they too might have the same aetiology (Irvine, 1999). For example, testicular cancer is four times more common in Denmark than Finland, while studies have shown that sperm counts are rather low in Denmark (Jensen *et al.*, 1996) and semen quality appears to be better in Finland (Vierula *et al.*, 1996). While the testicular cancer data are consistently collected across both time and registries, this cannot be said of the semen quality data. As will be discussed in the review of the semen quality literature, there are considerable inconsistencies between studies of semen quality, i.e. study participants, sample collection and analysis, meaning that comparisons between them are flawed.

Although the aetiology of testicular cancer is still largely unknown, some other risk factors have been identified. For instance, recent socio-economic changes have meant a higher intake of fat and a more sedentary lifestyle, both of which have been associated with testicular cancer, particularly during childhood (Buetow, 1995). Childhood trauma/injury and illness such as mumps and meningitis have also been found to increase the risk of testicular cancer, although recall bias can not be ruled out in relation to trauma/injury. Therefore, if *in utero* exposure to environmental chemicals does result in an increase risk in testicular cancer, there are other potential risk factors that might also contribute, and research identifying which risk factors are the most important has been limited.

Finally, as mentioned earlier CIS cells are known as precursors to testicular cancer and the aetiology of such cells might shed light on possible risk factors for the malignancy. It has been found that they originate during foetal life and that subnormal androgen exposure and/or increased oestrogen exposure are risk factors (Slowikowska-Hilczer, Walczak-Jedrzejowska, and Kula, 2001), so giving some credence to the *in utero* environmental exposure hypothesis. However, the reasons for and the biological mechanism for the development of these germ cells is still unclear.

### **2.2.1.3 Summary of previous research of testicular cancer**

There is evidence that the incidence of testicular cancer has increased over the last 60 years, however it is unclear why this has happened. There is evidence of an environmental/genetic interaction and that changes in socio-economic factors have resulted in some of the increase. It has been argued that the associations between testicular cancer and other conditions of male reproductive health are due to common aetiology, however this is not conclusive. Furthermore, while the aetiology of CIS cells, the precursors to testicular cancer, indicate an origin in foetal life and an association with hormones, their development and aetiology is largely unclear. Therefore, while there has been an increase in incidence in testicular cancer over time, it can not be shown that this is largely due to increasing *in utero* exposure to environmental chemicals.

## **2.2.2 Hypospadias**

The estimates of birth prevalence of hypospadias ranges from 0.2 to 2% (Kallen et al., 1986). As with testicular cancer there have been reports of an increase in the prevalence of the congenital malformation of the male genital tract hypospadias over time (Paulozzi, Erickson, and Jackson, 1997), however the evidence for this is not as conclusive as with the sarcoma. This section will provide an overview of previous research that show both an increase and decline in the prevalence of this condition and reflect on these differing results. However, firstly a description of hypospadias will provide an overview of the condition.

### **2.2.2.1 Morphology of hypospadias**

Hypospadias is an abnormality of the location of the urethral opening on the shaft of the penis. It is believed to be as a result of a congenital defect of the urethral development that occurs embryologically. As it is a congenital malformation it is usually detected at birth and treatment is surgical repair. Previously, surgery was carried out from age 3 years onwards, as the procedure would be technically easier with a larger penis. However, from the 1980's, most surgery has been carried out when the child is 6-18 months so as to limit possible emotional and psychological trauma (Duckett, 1998).



The most used classification of hypospadias is based on the location of the abnormal urethral opening as outlined by Duckett (1998). There are 3 classifications which are of increasing severity i.e. location from normality – anterior (glandular and subcoronal), middle (distal penile, midshaft and proximal penile) and posterior (penoscrotal, scrotal and perineal). The most common of these is anterior (50% of cases), followed by posterior (30%) and middle (20%), so the least severe of hypospadias cases are also the most common.

### **2.2.2.2 Epidemiology and aetiology of hypospadias**

The first reports showing increases over time in hypospadias prevalence came from birth defect monitoring programmes in different countries including several European countries, such as Norway (Bjerkedal and Bakketeig, 1975), Sweden (Kallen and Winberg, 1982), Denmark (Kallen *et al.*, 1986), England and Wales (Matlai and Beral, 1985) and also the United States (ICBDMS, 1991).

However the registering of hypospadias and other malformations has not been standard across registries and time, making comparisons across countries and time unreliable (Toppari, Kaleva, and Virtanen, 2001). In particular, the increasing sensitivity of surveillance systems might explain the apparent increase in cases, especially the least severe cases. As already mentioned the least severe cases are also the most common and so would make a greater impact on the prevalence rates.

But it is still not clear that the changing sensitivity of the surveillance systems would fully account for the entire temporal trend. In a retrospective review of two neonatal intensive care units (NICU) in Connecticut a 10-fold (0.4% to 4%) higher incidence of hypospadias admissions was found from 1987 to 2000. As these admissions to intensive care would have been more likely to be severe cases, it is argued that it is unlikely that increased sensitivity of reporting would have accounted for the changes over time. However, it is not clear if the threshold for ‘severe’ cases has also shifted and as the change in incidence in the NICU population is based on the percentage of admissions, shifts in admission policies for both hypospadias cases and other conditions might affect the admission rates.

Further analysis of the ICBDMs data mentioned previously highlighted the different experiences of hypospadias globally (Paulozzi, 1999). Those registries which saw



increases included Atlanta (from 17 cases per 10,000 births in 1968 to 31 cases per 10,000 births), Norway and Denmark (doubling of mild hypospadias cases in 1970s and 1980s) as well as other European countries and Japan. At the same time other systems did not experience these increases – California showed no upward trends, incidence actually fell in the 1980s in northern Netherlands and remained constant in China, Hungary, Mexico and South America. Furthermore, many of those systems that did show an increase in incidence appeared to plateau after 1985.

The author of this analysis did note that differences in registrations meant that it was unclear if increases in incidence had taken place. However, another study was able to show that geographical differences between rates of hypospadias could not wholly be explained by ascertainment differences. Seven malformation international surveillance systems were analysed and, on taking account of differences in ascertainment, still found geographical variations in the prevalence of hypospadias (Kallen *et al.*, 1986). This reported geographical variation in hypospadias has been used to argue that environmental and/or genetic factors are associated with this condition. However as it is not clear that the different surveillance systems are comparable then any conclusions based on any apparent differences are dubious.

The reported risk factors for hypospadias show that, as with testicular cancer, various potential mechanisms could result in this condition. In the previously mentioned descriptive epidemiological study of data concerning hypospadias from seven surveillance systems across the world, the study group found a correlation between hypospadias and increasing maternal age, parity, lower birth weight, shorter gestational age, seasonality and male-male twin births (both monozygotic and dizygotic) (Kallen *et al.*, 1986). Therefore while the *in utero* environment is associated with hypospadias, it is not clear that this milieu is only a result of environmental chemicals or also due to other socio-economic and life-style factors.

As already mentioned in relation to testicular cancer, hypospadias has been reported to be a risk factor for the development of this cancer (Prener *et al.*, 1996); also men with cryptorchidism and/or hypospadias were overrepresented among patients with testicular cancer (Giwerzman, Muller, and Skakkebaek, 1988). Furthermore, Kallen *et al.* (1986) found a correlation between the prevalence of isolated hypospadias at

birth and decreasing fertility in a population, it has also been reported that impaired semen quality was found in fathers of boys with hypospadias (Fritz and Czeizel, 1996). However as already discussed in relation to testicular cancer it is not possible to ascertain if these associations are due to a common environmental aetiology and/or due to other risk factors.

### **2.2.2.3 Summary of previous research of hypospadias**

Therefore, there is evidence that hypospadias might have increased in particular countries and that there are geographical differences in the rates. The possible risk factors for this condition point to the intrauterine environment and there is some evidence of a relationship between hypospadias and other conditions of male reproductive health.

However, any results from these reports are inconclusive due to data quality issues raised by the use of registry-based data. As recommended by Toppari *et al.* (2001), further epidemiological studies should be based on cohort data with standardised diagnostic criteria, and this has begun to be implemented. Also, if registry data are used that they are consistent in classification over time and a thorough assessment of data collection systems, from which the data are derived, should be carried out before their use.

## **2.2.3 Cryptorchidism**

Cryptorchidism is the most common congenital malformation presented with a birth prevalence estimated as ranging from 1 and 3%. As with hypospadias and testicular cancer there are reports showing increases in the incidence of this congenital malformation of the male genital tract (Ansell *et al.*, 1992). However, as with hypospadias the evidence is inconclusive.

### **2.2.3.1 Morphology of cryptorchidism**

Cryptorchidism literally means hidden or obscure testis and refers to an undescended or maldescended testis (Kolon, 2002). The most useful clinical classification of cryptorchidism is whether the testes are apparent upon physical examination. If not apparent the testes may be intra-abdominal or absent, while if palpable they may be undescended, ectopic or retractile. Treatment is dependent on the classification of cryptorchidism i.e. the presence and location of testes. In some cases manipulation of



the scrotum may resolve the problem and spontaneous descent of the testes can occur up to the age of 1 year. When one of these scenarios is not possible or does not occur then either hormonal treatment or surgery would be carried out, depending on the severity of the condition. Previously, these treatments were carried out at older ages than the now usual age of approximately 1 year (Docimo, 1995). This reduction in the age of treatment is in response to the evidence that spontaneous descent rarely occurs after 1 year and that earlier treatment results in improved fertility.

Unlike the other congenital malformation hypospadias, cryptorchidism is not always identified at birth. Furthermore, as we have already seen spontaneous descent of the testes can occur up until the boy is 1 year. These elements of its morphology have an impact on the results of previous research of cryptorchidism epidemiology.

### **2.2.3.2 Epidemiology and aetiology of cryptorchidism**

The body of evidence showing an increase in prevalence of cryptorchidism is not as strong as that for hypospadias. One of the first published studies of cryptorchidism has been used as a reference point for future work as case ascertainment was assessed as accurate as they were based on well-defined classifications (Scorer, 1964). He found that the percentage of boys born in a London hospital with cryptorchidism was 21% for those boys born weighing less than 2,500g, while 2.7% of boys born weighing 2,500g and more were identified with cryptorchidism. These children were followed for one year and at 3 months the relevant percentages had reduced to 1.7% and 0.9% respectively.

Following on from this research, that identified that low birth weight is associated with cryptorchidism, a larger UK study that used the same criteria showed that the cryptorchidism rate at birth had increased by 35.1% and at 3 months by 92.7% over the 30 years from the 1950s (Ansell *et al.*, 1992).

However, other studies of international data do not mirror these results. Paulozzi's (1999) analysis of the ICBDMs data for hypospadias, as discussed previously, also included analysis of the equivalent cryptorchidism data. This analysis showed even greater differences between countries in the temporal trends of cryptorchidism compared to hypospadias. In South America and Denmark increases over time were shown, and while increases were found in the U.S in the 1970s and 1980s the rates



have fallen there since 1985. Furthermore, no changes in incidence were found in the 20 years from 1976 in either Norway or France.

The cryptorchidism data, like the hypospadias data, has limitations as it also based on registry data (Toppari *et al.*, 2001), so any comparisons across both time and geography are constrained in what conclusions can be made. This can be underlined by results from Paulozzi (1999) on cryptorchidism rates in England. While rates initially rose, they fell from 1990 onwards, probably due to the tightening of inclusion criteria at the same time.

Another issue that will have affected the recorded rates of cryptorchidism over time and between surveillance systems is the morphology and natural history of cryptorchidism. As cryptorchidism is not always identified at birth and testes can spontaneously descend, case ascertainment depends on individual clinician's practice. For example, mild cryptorchidism might be identified at birth or not, and if identified the clinician may not record as they might wait to see if it persists. It would appear that these potential ascertainment differences are less relevant to identifying a hypospadias case, as it is more clearly identified at birth and largely treated with surgery (Duckett, 1998). Therefore although problems have been identified with the ascertainment of hypospadias cases, the problems appear to be more acute with the cryptorchidism data.

Although even less research has been published on the aetiology of cryptorchidism it, like hypospadias, appears to be associated with the *in utero* environment. But, as like hypospadias, it is not clear what is causing the changes *in utero* - chemicals, socio-economic or life-style factors. Two studies have suggested that possible risk factors for cryptorchidism include maternal obesity, low birth weight, preterm delivery, the presence of other congenital malformations, ethnic group and a family history of the condition (Berkowitz *et al.*, 1995; Berkowitz and Lapinski, 1996). Furthermore, a strong association between cryptorchidism and low social class has been suggested (Moller and Skakkebaek, 1996).

### **2.2.3.3 Summary of previous research of cryptorchidism**

There are strong reservations concerning the results showing increases in cryptorchidism rates, and these appear to be more well-founded than concerns over hypospadias data. Therefore it is more pertinent that the recommendations of Toppari *et al.* (2001), concerning the collection of hypospadias and cryptorchidism data in further epidemiological studies should be adhered to. Until these more consistent data are presented we can not be sure that any temporal increase in cryptorchidism has occurred. Furthermore, as there are differences in the registry data, any geographical differences that might be found would be suspect. Therefore, consistently collected cryptorchidism data would mean it is possible to investigate more reliably differences over geography and time.

Finally, while the little research carried out on the possible risk factors for cryptorchidism point to the intrauterine environment, it is not clear if this is a result of environmental chemicals, socio-economic or lifestyle factors.

### **2.2.4 Decline in Semen Quality**

Much of the controversy that surrounds the postulated decline in male reproductive health stems from the reporting of a secular decrease in semen quality. While the reporting of a temporal decline in semen quality in itself would cause controversy, the research carried out raised questions and debate. This research project does not include analysis of semen quality data; however this discussion of previous research highlights the outstanding issues in relation to male reproductive health generally.

The debates stem from the first meta-analysis of worldwide semen quality in normal men (Carlsen *et al.*, 1992). Exclusions from the meta-analysis were data on infertile couples, men selected on the basis of their fertility and data generated using non classical approaches to semen analysis. Data included have been published in 61 English language papers between 1938 and 1990, and there were semen results for 14,947 men. The meta-analysis found that sperm concentration had declined from  $113 \times 10^6/\text{ml}$  in 1940 to  $66 \times 10^6/\text{ml}$  in 1990. It was also reported that the average age of the men studied did not change with time and that age appeared to have no influence on the observed secular trend. The authors hypothesised that racial,



geographical and other factors could explain these changes over time; although they did concede that there were methodological limitations to the analysis.

The publication of this analysis ignited the debate about the possible decline in semen quality. However, a debate was ignited about the report itself. In particular about the data used and the analysis carried out. Several papers were published following this report that provided reanalysis and reinterpretations of these data which highlighted several criticisms. These included the inappropriate use of linear regression and issues inherent to meta-analysis i.e. differences in subject selection/recruitment, time periods and laboratory methodology between studies, as well as the potential for controlling for confounding variables (e.g. age of men and abstinence time) being limited (Brake and Krause, 1992; Bromwich *et al.*, 1994; Farrow, 1994; Olsen *et al.*, 1995).

Following these papers, part of the data from the Carlsen 1992 paper were re-analysed which took account of the criticisms (Swan, Elkin, and Fenster, 1997). The analysis used 54 of the 61 studies used in the original paper and carried out logistic regression that attempted to control for abstinence, age, proven fertility, different semen sample collection methods and location. The aim of this analysis was to examine geographical differences in semen quality and any associations between region and year – differing results were found depending on region. While a significant decline in semen density in the United States and Europe, albeit not to the same extent as in the Carlsen 1992 paper, there was no such pattern in non-Western countries. A further expansion of the meta-analysis was carried out by the same research group three years later (Swan, Elkin, and Fenster, 2000), which included a further 47 studies. They found the same average decline in sperm count as reported by Swan *et al.*, (1997).

Several other studies were carried out following the Carlsen 1992 meta-analysis but they too have failed to come to a consensus. (Auger *et al.*, 1995) analysed semen data from 1,750 men in Paris of proven fertility resulting from consistent methods of recruitment and laboratory techniques. As well as showing a decrease over time in all the classical parameters of semen quality they were also able to look at the effect of age and year of birth while taking account of other factors that may affect sperm



concentration, such as abstinence. They still found a reduction of 2.6% in sperm concentration with each year of birth and less dramatic reductions in other parameters of semen quality. In Scotland of 577 unselected candidate semen donors born between 1951 and 1973, the median sperm concentration decreased from  $98 \times 10^6/\text{ml}$  from donors born before 1959 to  $78 \times 10^6/\text{ml}$  from donors born after 1970 (Irvine *et al.*, 1996).

Recently, a study of Danish military conscripts aged 18-20 showed a high proportion of sub-optimal semen quality (Andersen *et al.*, 2000). Of those of the 708 men who had no history of reproductive disease and abstinence was at least 48 hours, 18% had sperm concentrations below 20 million per ml and 40% were below 40 million per ml. The median sperm concentration of those men with abstinence more than 48 hours was 45 million per ml. Another Danish study, showed similar results for the same age group and was able to compare this to older men, so showing an age cohort effect (Bonde *et al.*, 1998). From the 1,196 men who donated semen sampled over time for occupational health research, those men in the 18-20 year old cohort (i.e. born 1976-79) had a median sperm concentration of 41 million per ml. Furthermore, those men born in the years 1937-49 had a median sperm concentration of 63 million per ml compared to those men born in 1970-74 who had a median sperm concentration of 52 million per ml.

However, other studies did not find a decrease over time in semen quality. In an analysis of volunteer sperm donors in Toulouse between 1977 and 1992 there appeared to be no change over time in mean sperm concentrations when the age of the donors was accounted for (Bujan *et al.*, 1996). Another analysis of volunteer semen donors, this time in Australia between 1980 and 1995, found no effect on median sperm concentration; total sperm number; or ejaculate volume; from year of observation or year of birth (Handelsman, 1997).

While other studies have shown a decline in semen quality in Denmark, another study investigating unselected semen donor candidates between 1977 and 1995 found the opposite (Gyllenberg *et al.*, 1999). Although sperm motility declined over this time, there appeared to be no change in other semen quality measurements including semen volume and percentage motile. Furthermore, the mean sperm

concentration actually rose from 53 million per ml in 1977 to 72 million per ml in 1995.

Two recent studies from the Far East have shown higher mean sperm concentrations than Western studies and no secular trends or association with age (Itoh *et al.*, 2001; Seo *et al.*, 2000). Itoh *et al.* (2001) found no decline in semen quality between two groups of healthy volunteers in 1975-80 and 1998 in Sapporo, Japan; and no association between age in either group was found. The mean sperm concentration for the 1975-80 group was 70.9 million per ml compared to 79.6 million per ml for the 1998 group. In Korea between 1989 and 1998 the 22,249 men who presented with infertility showed no temporal trends in semen concentration and no association with age or year of birth.

Therefore, the research carried out on temporal trends in semen quality is inconclusive. The doubts that remain are largely due to the studies that have been carried out. For example, a number of the studies mentioned above have used particular groups of the population – semen donors, volunteers, men with proven fertility, men presenting with infertility, vasectomy patients and military conscripts. Would these men represent the general male population and would in fact have there own inherent biases? As discussed by Handelsman (1997), the use of data from self-selected subjects could introduce considerable biases to the results which would mean they would not always be generalisable to the general population. Some of these studies did attempt to overcome these potential biases. Anderson *et al.*'s (2000) study of Danish military conscripts was able to show that their volunteers were representative based on place, year of birth and educational status.

Problems also arise with these studies of semen quality when data from different locations using different techniques and methods results are compared. While Fisch *et al.* (1996) found a small but significant increase in the sperm concentration over time in 3 locations in the USA between 1970 and 1974, they also found differences between the locations. The highest concentrations was found in New York (mean =  $131.5 \times 10^6/\text{ml}$ ), then Minnesota ( $100.8 \times 10^6/\text{ml}$ ) with the lowest being in California ( $72.7 \times 10^6/\text{ml}$ ). While it could be suggested that the geographical variation in semen concentrations could have been due to geographically varying environmental factors



and/or genetic pre-disposition, it is unclear because, as noted by the authors, there were differences in the laboratory techniques and data analysis, between the 3 locations. There same difference in date could explain the reported difference across time and country/location seen in the other studies described.

Finally, many of these studies are retrospective meaning that controlling for important confounder can be limited. For example, Gyllenborg *et al.*'s (1999) analysis of unselected semen donor candidates between 1977 and 1995 was based on anonymised records so it was not possible to control for age, a possible confounder. Therefore the reported stability in the temporal trends found could be due to the different ages of the donors between the time periods.

As recommended by (Irvine, 2001), future research both on the temporal trends and possible aetiology of semen quality should be prospective and be carried out on randomly selected men. Furthermore, that the analysis and collection of the semen samples should be consistent. In fact, a population study of semen quality has just been completed in Scotland which aimed to overcome these issues. The Scottish Male Reproductive Health Study hopes to report on its findings within the next year (2005).

While most studies of semen quality have concentrated on assessing temporal trends, some have looked at the possible aetiology. As already mentioned, Fisch *et al.* (1996) found differences in semen concentration between the 3 US locations but it could not be concluded that these differences were genuine or not due to differences in data collection and analysis. However, another study comparing semen quality across Europe did find geographical variation (Jorgensen *et al.*, 2001). Although the data was from men whose partners were pregnant, so a particular sub-group, any inter-laboratory differences were assessed and the subsequent analysis was standardised. On standardising to a 30 year old, with abstinence of 96 hours, sperm concentrations were estimated for both winter and summer as, seasonal variations had been found, these estimates are shown in Table 1.



**Table 1** Sperm concentrations (million per ml) by European City and Season for 30 year old man who has abstained for 96 hours – data reproduced from Jorgensen *et al.*, (2001)

European City	Sperm concentration (million per ml)	
	Winter	Summer
Turku	132	93
Edinburgh	119	84
Paris	103	73
Copenhagen	98	69

While all have lower concentrations in the summer compared to the winter, there are consistent differences between the four cities, which led the authors to conclude that these results may indicate different environmental exposures or lifestyle changes in the four populations. Furthermore, as we have also seen two studies from Far East did not show temporal trends in semen quality but reported higher mean sperm concentrations than comparable Western studies (Itoh *et al.*, 2000; Seo *et al.*, 2000). So there is some evidence of regional differences in semen quality. It has been hypothesised that these regional differences might be due to ethnic, environmental or lifestyle factors and so could be used to investigate the aetiology and temporal changes of semen quality (Irvine *et al.*, 1996).

### 2.3 Testicular dysgenesis syndrome (TDS)

As shown previously, there is some evidence, of varying vigour, that testicular cancer, hypospadias, cryptorchidism and semen quality have shown adverse temporal trends. This combined body of evidence has led some researchers to hypothesise that one common aetiology could be causing these reported deteriorations in different condition/diseases of male reproductive health. Known as the ‘oestrogen hypothesis’, Richard Sharpe and Niels Skakkebaek proposed that increased *in utero* exposure to oestrogens and/or anti-androgens might be related to the increase in male reproductive anomalies (Sharpe and Skakkebaek, 1993). Since then, this hypothesis has been further elaborated upon; it is postulated that these adverse trends may in fact reflect an increasing number of men suffering from varying degrees of one underlying entity - Testicular dysgenesis syndrome (TDS) (Skakkebaek, Rajpert-De Meyts, and Main, 2001).

### 2.3.1 Development of TDS hypothesis

The first researchers who hypothesised that the *in utero* environment of the foetus might be associated with resulting anomalies in male reproductive health, did so in relation to testicular cancer (Henderson *et al.*, 1979; Depue, Pike, and Henderson, 1983) and cryptorchidism (Depue, 1984). Following the increase in papers showing a decline in semen quality, and an increase in testicular cancer and the congenital malformations cryptorchidism and hypospadias, this hypothesis was expanded upon in relation to all these anomalies (Sharpe and Skakkebaek, 1993).

Sharpe and Skakkebaek proposed that increased *in utero* exposure to oestrogens might be related to the increase in all the male reproductive anomalies through two primary oestrogenic mechanisms;

- (i) suppression of gonadotrophin hormones;
- (ii) impairment of Leydig cells development.

Gonadotrophins are protein hormones involved in reproductive activity that stimulate the gonads and primarily act on the sertoli and leydig cells. The sertoli cells manage and control the development of spermatogenesis i.e. production of sperm. The leydig cells produce testosterone, the principal testicular androgen, which has a key role both in the early development of the male reproductive system and the reproductive and sexual function of the adult male (Johnson and Everitt, 2000).

Many chemicals that humans ingest have been found to have oestrogenic properties including, industrial chemicals such as; particular herbicides, fungicides, insecticides, nematocides, organophosphates, heavy metals, PCBs and phthalates (ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), 1996).

Since this hypothesis, further work has been carried out both in human and animal studies and so further potential mechanisms producing damage to the male reproductive health system have been proposed (Skakkebaek, Rajpert-De Meyts, and Main, 2001). It is hypothesised that while it is possible that these environmental pollutants have oestrogenic properties as detailed previously they are more likely to



have anti-androgen properties that inhibit the normal reproductive tract development in the male.

These potential anti-androgenic mechanisms include;

- (i) suppression of androgen production
- (ii) suppression of androgen receptor expression
- (iii) suppression of secretion of insulin-like factor-3 (InsL3) by foetal Leydig cells.

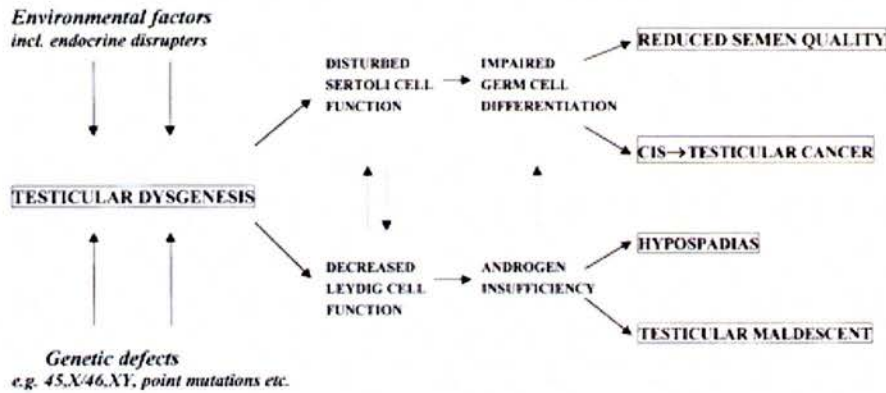
As already discussed androgens play a key role in the development and function of the whole male reproductive system so the suppression of its production and its receptors would impair the system and conditions in different ways. InsL3 acts on the gubernaculum of the testis which plays a key role in guiding the testis during its transabdominal descent. Therefore the suppression of this factor could induce cryptorchidism.

Both natural and synthetic substances have been found to have anti-androgen properties. Particular substances that occur naturally in plants known as phytoestrogens have been found to have both oestrogenic and anti-androgenic properties (Colborn, Vom Saal, and Soto, 1993). Medications such as diethylstilbestrol, ethinyl estradiol and tamoxifen; and industrial chemicals such as DDT, p-nonylphenol and bisphenol A have been found to have anti-androgenic properties (Greim, 2004).

In the same paper Skakkebaek and colleagues further expanded on the 'oestrogen hypothesis'. They proposed that the reports showing a decline in semen quality, increases in testicular cancer, cryptorchidism and hypospadias are symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS), which may be increasingly common due to increases in environmental factors. Within the paper they illustrated this hypothesis with two diagrams. Firstly, Figure 1 shows the diagram from the paper explaining the genetic and environmental pathways to the various manifestations of TDS.



**Figure 1** Schematic representation of pathogenetic links between the components and clinical manifestations of testicular dysgenesis syndrome – reproduced from Skakkebaek *et al.*, 2001.

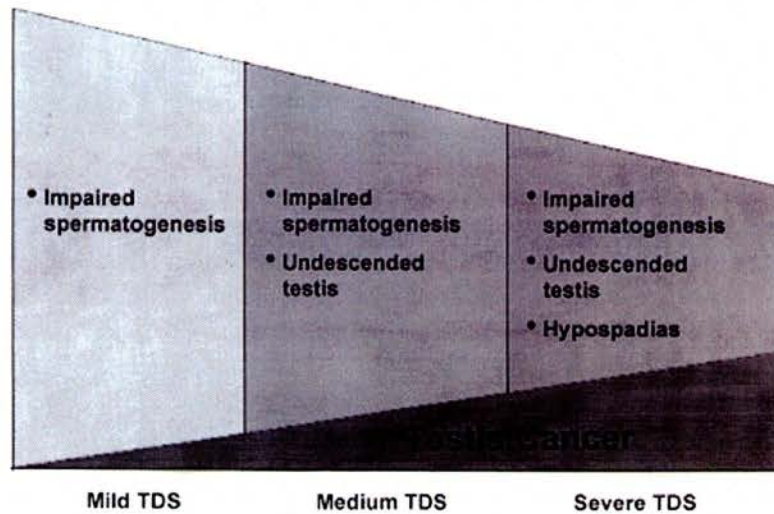


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As can be seen, the impact of both genetic susceptibility and exposure to environmental factors results in TDS. In turn this syndrome affects different aspects of the male reproductive system, which in turn results in the manifestation of different conditions. For example, the disruption of sertoli cells resulting from the anti-androgen effect of the oestrogens impairs the differentiation of germ cells. These impaired germ cells could result in two outcomes. As they are involved in spermatogenesis then semen quality could be impaired, also these damaged germ cells could develop into the non-malignant germ cells known as carcinoma-in-situ (CIS). As previously described, CIS cells have been found to be precursors to testicular cancer (Słowikowska-Hilczer, Walczak-Jedrzejska, and Kula, 2001).

While explaining the potential pathways from TDS to the particular conditions related to male reproductive health, the authors proposed that differing severity of TDS results in the manifestation of different symptoms/conditions. Figure 2 illustrates the proposed relationship between the relative frequencies of the various symptoms of TDS. The authors propose that while the overall incidence of TDS decreases with its severity, the relative incidence of testicular cancer increases while the relative incidence of the other conditions decrease.

**Figure 2** Illustration of the relationship between the relative frequencies of various symptoms of the testicular dysgenesis syndrome (TDS) – reproduced from Skakkebaek et al., 2001.



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While the principal aim of the Skakkebaek and colleagues (2001) paper was to outline the proposed hypothesis, from an epidemiological framework it also appears to attempt to prove causality, i.e. that *in utero* exposure to oestrogens and/or anti-androgens results in various symptoms of TDS. The criteria for inferring causality as outlined by Bradford Hill (Hill, 1965) are:

- (i) Strength of the association – The stronger an association, the less it could merely reflect the influence of some other aetiological factor(s). This criterion includes consideration of the statistical precision (minimal influence of chance) and methodological rigor of the existing studies with respect to bias (selection, information, and confounding).
- (ii) Consistency – replication of the findings by different investigators, at different times, in different places, with different methods and the ability to convincingly explain different results.
- (iii) Specificity of the association – there is an inherent relationship between specificity and strength in the sense that the more accurately defined the disease and exposure, the stronger the observed relationship should be.
- (iv) Temporality – the ability to establish that the putative cause in fact preceded in time the presumed effect.



- (v) Biological gradient – incremental change in disease rates in conjunction with corresponding changes in exposure. The verification of a dose-response relationship consistent with the hypothesized conceptual model.
- (vi) Plausibility – we are much readier to accept the case for a relationship that is consistent with our general knowledge and beliefs. Obviously this tendency has pitfalls, but commonsense often serves us.
- (vii) Coherence – how well do all the observations fit with the hypothesised model to form a coherent picture?
- (viii) Experiment – the demonstration that under controlled conditions changing the exposure causes a change in the outcome is of great value, some would say indispensable, for inferring causality.
- (ix) Analogy – we are readier to accept arguments that resemble others we accept.

The authors have provided various examples of changes in male reproductive health (criteria (ii)), a hypothesis to explain the biological pathways from environmental and genetic factors to TDS and the various conditions of male reproductive health (vi) and how the observed changes fit the hypothesis (vii). They also attempt to show that varying exposure results in varying degrees of the syndrome and conditions (v) and that from animal studies change in dose of chemicals results in varying conditions (viii).

Although these criteria have been touched upon in the Skakkebaek *et al.* (2001) paper, an examination of the criteria in relation to current male reproductive health research provides an insight into the remaining questions surrounding it.

While there are numerous reports showing a decline in male reproductive health in terms of a decline in semen quality and increases in the rates of testicular cancer, cryptorchidism, and hypospadias (ii), very little work has been done on assessing the methodological rigor of this existing evidence (i). In fact, a number of concerns about the available reports have been highlighted and have been discussed in the examination of the known aetiology of the conditions. Therefore, the evidence used to show a decline in male reproductive health is inconclusive and so inferences made between the changes in conditions and possible risk factors must also be open to doubt (vii). Furthermore, as will be seen in the next section the many potential



pathways of exposure for these conditions mean that the strength and specificity of the association is ambiguous.

### **2.3.2 Human Exposure to Endocrine disruptors**

The TDS hypothesis postulates that exposure to environmental oestrogens and/or anti-androgens *in utero* have resulted in a decline in the male reproductive health. While the previous section outlined how these chemicals, known as endocrine disruptors, are conjectured to result in changes in the male reproductive health system; this section will outline how humans are believed to be exposed to these environmental chemicals.

Endocrine disrupter research is a large and complex field and so only a small part of this research is discussed here. This section concentrates on the possible routes of exposure to the foetus, as it is postulated that the exposure to environmental chemicals *in utero* results in TDS.

There are various substances that are suspected of being endocrine disruptors although little direct clinical data to verify these concerns (Hester and Harrison, 1999). They are both naturally occurring and anthropogenic chemicals, with the most important in terms of human health and their main sources of human exposure shown in Table 2.

This table shows that even when only identifying the key known or suspected endocrine disruptors, there are various possible sources of exposure. However there are key sources of human exposure, the most important being food. While the majority of endocrine disruptors in food are naturally occurring phytoestrogens (plant compounds) there are other sources of these chemicals in what we eat (Safe, 1995). For example, natural hormones such as oestrogens, progesterones and testosterone are found in eggs and meat and dairy products, but these can be further enhanced due to the use of hormones by vets and as growth enhancers (Hartmann, Lacorn, and Steinhart, 1998). Furthermore, packaged food can contain these compounds due to leeching from particular containers (e.g. phthalates and bisphenol A). Pesticides that have not been used for a number of years can still be found in

food produced in areas where they were last used (UK Ministry of Agriculture Fisheries and Food and Health and Safety Executive, 1997).

**Table 2 Key known or suspected endocrine disruptors**

Compound	Source of Human Exposure
Natural and synthetic hormones	Natural hormones, augmented by hormonal drugs such as those used as oral contraceptives, are excreted by humans and animals and occur in sewage
Phytoestrogens	Natural constituents of many foodstuffs including herbs, grains and seeds, vegetables, beans and fruits
Mycotoxins	Produced by fungi that can contaminate crops
Organochlorine pesticides	Common persistent environmental pollutants include DDT, lindane and beta-HCH
Polychlorinated biphenyls (PCBs)	Widespread environmental chemicals
Alkylphenol polyethoxylates (APEs)	Used in detergents, paints, herbicides, pesticides and plastics. Breakdown products, such as nonylphenol and octylphenol, are found in sewage and industrial effluents
Dioxins	Products of combustion of many materials
Phthalates	Widely used in consumer products such as cosmetics, toiletries, perfumes and medical products. Used widely in plastic packaging and can leech into the food in small quantities
Bisphenol A	Component of polycarbonate plastics and epoxy resins used to line food cans which again can leech into contents

Drinking Water is also believed to be a potential source of human exposure to endocrine disruptors, and this is a result of various mechanisms. Firstly, pharmaceutical drugs and their metabolites find their way into the environment chiefly via excretion into sewage (Arcand-Hoy, Nimrod, and Benson, 1998). Furthermore, groundwater can be contaminated by chemicals carried by rainwater, from leaching of waste sites or waste water carrying industrial or agricultural waste. Some but not all of these contaminants can be removed by water treatment. While surface water, rivers and lakes and the sea are very vulnerable to contamination by waste and airborne pollutants, the air itself can be a source of endocrine disruptors (Hester and Harrison, 1999). Products of combustion, such as dioxins and polycyclic aromatic hydrocarbons, are possible endocrine disruptors (Clemons *et al.*, 1998).

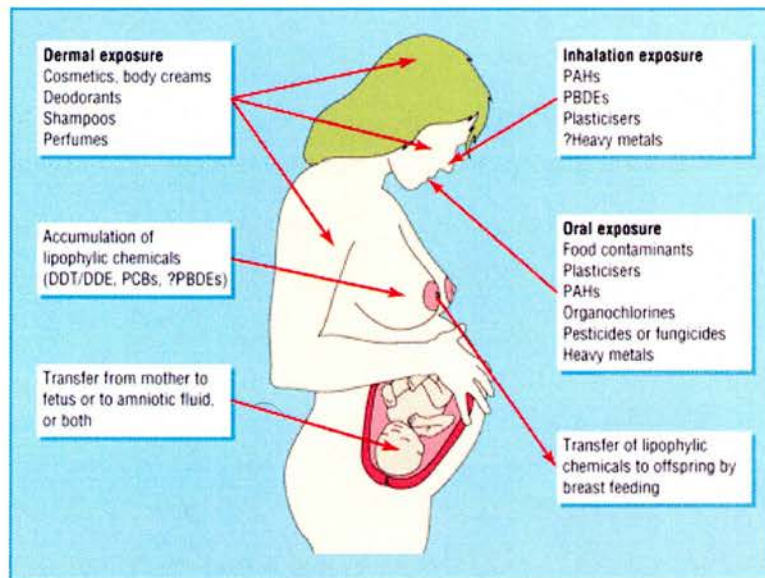
Finally, another potential source of exposure by humans to endocrine disruptors is occupation. Inorganic chemicals such as lead, manganese and mercury, and organic ones such as dibromochloropropane (DBCP), ethylene glycol and carbon disulfide are believed to produce adverse effects on male reproductive health (Tas, Lauwerys,



and Lison, 1996). However it is not clear if these effects are due to endocrine disruption or primarily the chemical itself, and not other confounding factors related to lifestyle (smoking, alcohol, and diet) or socioeconomic status.

So even for only some of the common environmental chemicals the potential routes of exposure to the mother and to the foetus are various (Figure 3) (Sharpe and Irvine, 2004).

**Figure 3** Routes of human exposure to some common environmental chemicals\*  
- reproduced from Sharpe and Irvine (2004)<sup>1</sup>



\* DDE=1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene

DDT= dichlorodiphenyltrichloroethane

PAHs=polycyclic aromatic hydrocarbons

PCBs=polychlorinated biphenyls

<sup>1</sup> Reproduced with permission from the BMJ publishing group

This illustration, in Sharpe's and Irvine's clinical review of the evidence to link environmental chemicals and human reproductive health, highlights the complex issue of attempting to identify the mechanisms by:

- (i) which humans are exposed to these environmental chemicals,
- (ii) how these chemicals are transferred to a foetus, and
- (iii) how this exposure manifests as particular conditions.

For example the mother could have been exposed to some of these chemicals through-out her lifetime which could bioaccumulate (i.e. build up in the body) in tissue or she could be exposed to particular chemicals while pregnant. These



chemicals could accumulate in the amniotic fluid or be transferred to the baby postnatally via breast feeding. The myriad potential pathways for exposure of the mother and transfer to the foetus/baby have meant it has been very difficult to show exactly how exposure to these chemicals has resulted in various degrees of the testicular dysgenesis syndrome.

Furthermore, measuring the foetal exposure to environmental chemicals and then relating this to various disorders is not only logistically problematic it is compounded by when the conditions manifest themselves. This is particularly pertinent to those conditions which occur decades later than the proposed exposure i.e. testicular cancer and poor semen quality, but is also relevant to a lesser extent to those conditions that manifest themselves at birth i.e. cryptorchidism and hypospadias. Table 3 shows that even for those conditions that manifest at birth the potential risk factors are numerous and include non-environmental ones.

**Table 3 Potential risk factors for the conditions of testicular dysgenic syndrome**

Time-Line	Risk Factor	Hypo-spadias	Crypt-orchidism	Testicular cancer	Poor semen quality
Conception	Parental Genetics	✓	✓	✓	✓
	Maternal bioaccumulation of potential environmental chemicals	✓	✓	✓	✓
	Maternal bioaccumulation due to other non- environmental risk factors (e.g. lifestyle)	✓	✓	✓	✓
In utero	Maternal biological response to pregnancy	✓	✓	✓	✓
	Maternal exposure to potential environmental chemicals while pregnant	✓	✓	✓	✓
	Maternal life-style factors while pregnant (e.g. smoking, diet)	✓	✓	✓	✓
Childhood	Breast feeding			✓	✓
	Illness in childhood (e.g. mumps)			✓	✓
	Childhood exposure to potential environmental chemicals			✓	✓
Adulthood	Adult lifestyle factors (e.g. smoking, heat exposure)			✓	✓
	Exposure to potential environmental chemicals (e.g. occupational)			✓	✓

Furthermore, these pathways overlap e.g. maternal genetics might impact on a woman's biological response to a pregnancy and so result in increased levels of hormones. Therefore, teasing out environmental chemicals role in affecting male

reproductive health is difficult, not only because there are other known risk factors for each of these conditions but also that all can occur at various times before manifestation of the condition.

Also, investigations to explain how these environmental chemicals affect the male reproductive system are further complicated by the fact that most of these potential toxicants are found at low concentrations within humans. For instance, the oestrogenic potency of synthetic substances such as 4-octylphenol and bisphenol A was more than 3,000 fold and 30,000 fold respectively, lower than that of endogenous estradiol (Sonnenschein *et al.*, 1996). It is unlikely that a toxicologically relevant effect could occur as a result of low potency and currently, little evidence has been provided to show that low concentrations of these environmental chemicals are found to result in changes to humans either foetally or long term into adulthood (Greim, 2004).

Furthermore, there are various factors that could affect an individual's susceptibility to these potential toxicants (Brent, 2004). This makes it difficult to show that a particular substance has teratogen properties i.e. produces abnormalities in the embryo or foetus by disturbing maternal homeostasis or by acting directly on the foetus *in utero* (Last, 2001). For instance, the timing of exposure *in utero* is crucial as the type and risk of malformation caused will vary both by the chemical and when the exposure occurred and at what dose. In addition, the physiological response of the mother will influence the teratogenic effects of any exposure and while this will be different between women it will also alter within a pregnancy.

This complexity has meant that describing how the exposure to these environmental chemicals then develops into the various conditions of testicular dysgenesis syndrome hypothesis is difficult and as yet has not been accomplished. Indeed, several evaluations of the evidence for adverse health effects resulting from exposure to endocrine disruptors have concluded that while temporal declines in the conditions related to the male reproductive tract have been reported, no direct causative role for low-level endocrine disruptors have been determined (Damstra *et al.*, 2002; GDCh-Advisory Committee on Existing Chemicals (Beratergremium für Altstoffe: BUA), 2002).



## 2.4 Conclusions of previous male reproductive health research

From previous research there is strong evidence of a temporal increase in the incidence of testicular cancer. There is also some evidence to show an increase in the incidence of hypospadias, although this is not as strong as that provided for testicular cancer due to quality issues surrounding the data used. However, the evidence provided to show a decline in semen quality or an increase in cryptorchidism is the least robust, and so it still unclear if temporal changes have occurred in these conditions. Therefore as this evidence was used to argue that an environmental factor is a result of these changes, the basis for this hypothesis could be seen as flawed. Until these issues are resolved with robust data, questions will remain. For instance any geographical differences found could be argued to be a result of differences in data used. Therefore future research either looking at the temporal or geographical differences in these conditions must address the concerns raised in relation to the quality and collection of the data used.

So, in order to look at geographical differences and so explore if a geographically varying environmental factor is associated with these conditions, consistently collected high quality data must be used. Furthermore, as we have seen various other risk factors unrelated to the proposed *in utero* environmental exposure are associated with these conditions. Therefore, so as to fully examine the geographical differences in these conditions and so investigate if a geographical varying *in utero* environmental risk factor is associated with them, then these other factors must be accounted for.

Finally, if these conditions are a result of one entity, TDS, we would expect to see associations between them. In fact Skakkebaek *et al.*, (2001) recommended that future epidemiological studies on trends in male reproductive health should take into account all aspects of TDS rather than focusing on only one symptom, as important biological information could be lost. At this time this appears to have not been carried out. Furthermore, no direct causative association between these environmental chemicals and the various conditions of male reproductive health has as yet been shown.



## **Chapter 3 : Outline and Methods of Research Project**

### **3.1 Introduction**

The previous chapter has put the concerns in relation to male reproductive health into context and highlighted unresolved issues. This chapter describes the research project carried out and how it proposes to answer some of the outstanding issues raised by previous research.

Firstly the aims of the research project are outlined, and the justifications and hypotheses that underlie these aims are discussed. As a key theme of the research project is spatial epidemiology, its concepts are then introduced and how they are applied to the study is discussed. This introduction of the concepts of spatial epidemiology is done before the data and methods are outlined as these concepts have implications for the research project.

The datasets used in the research project are classified into four categories depending on their use within the research project. As the datasets are from different time periods and so different geographies the methods used to establish them at one common geography is then described.

The methods used to achieve the aims of the research project can be found in three sections. The first summarises the methods used to describe the geographical variation of the three disease/conditions as counts per postcode sector; while the second outlines the spatial analysis of information pertaining to the cryptorchidism cases. The final methods section shows how the three disease/conditions were analysed conjointly. As the analysis outlined in the methods sections was carried out using the WinBUGs, this Bayesian analysis package and how it is used is also described.

The final section gives a summary of the chapter to provide a synopsis of the research project.

## 3.2 Aims and Objectives of Research Project

The aims of the research project are to:

- (i) Describe the geographical distributions of three indicators of male reproductive health in Scotland (i.e. testicular cancer, cryptorchidism and hypospadias).
- (ii) Describe the conjoint geographical distribution of the three indicators specified in (i).
- (iii) Identify explanatory factors that might account for the geographical distribution of male reproductive health in Scotland.

As discussed in Chapter 2, it is hypothesised that increasing *in utero* exposure in environmental oestrogens and/or anti-androgens has resulted in a decline in male reproductive health (Skakkebaek, Rajpert-De Meyts, and Main, 2001). If geographically varying environmental factors are associated with these diseases/conditions then we might see variations in the distributions of each of the disease/conditions across areas in Scotland. Therefore, the first aim of the research project aims to assess the geographical distributions of the disease/conditions across Scotland, to establish whether spatial variations exist. If variations are found, it would lend weight to the environmental exposure hypothesis, provided that the environmental factor also varies geographically.

The second aim of the research project is to look at the geographical distribution of the three indicators jointly. In a multi-indicator model, diseases have the potential to ‘borrow strength’ from each other and so reduce the variability of risk estimates within a particular postcode sector. Furthermore, if these diseases/conditions are believed to have one underlying environmental cause, as proposed by Skakkebaek, Rajpert-De Meyts, and Main (2001), then it is likely their geographical variation would be similar to each other. Therefore, the conjoint analysis of these diseases/conditions would examine the relationships between the spatial distributions of the three diseases/conditions. If a spatial relationship is found between them then this would also provide evidence of geographically varying environmental factor(s) being associated with all three conditions, i.e. a common aetiology.



While the first two aims of the research project attempt to assess if there is a spatial variation in these three disease/conditions, they do not attempt to explain these variations. It is useful in itself to describe the spatial variation of the disease/condition risk, and so indicate possible aetiology. However, the further analysis of the geographical variation of the diseases/conditions, by including potential covariates in the models, would not only identify possible explanatory factors but might also account for any spatial variation due to non-environmental factors. As discussed in Chapter 2, other risk factors unrelated to the intra-uterine environment exposure hypothesis are also associated with these conditions. Therefore, in order to fully examine the geographical differences of these conditions and so begin to investigate if a geographical varying environmental risk factor is associated with them, all known and available potential risk factors should be examined.

Also discussed in Chapter 2 was that previous research on male reproductive health anomalies have been inconclusive in part due to the quality of the data used, particularly in relation to cryptorchidism and semen quality, and to a lesser extent hypospadias. In contrast, data on testicular cancer, cryptorchidism and hypospadias in Scotland have all been collected consistently over geography and time; further details on these datasets are given in 3.4. The use of high quality data in this research project aims to address one of the unresolved criticisms of previous research on male reproductive health. With use of potentially consistently collected data, this research project will be able to examine geographical differences without the potential bias of differences in ascertainment over geography and time.

A further criticism of previous research on male reproductive health is that the assessment of the geographical variations of these diseases/conditions has largely been limited to comparisons of registries/countries, which are unreliable as there are usually differences in ascertainment. While there does not appear to be any analysis of the spatial variation of cryptorchidism and hypospadias, there has been spatial analysis of testicular cancer in the Great Britain. As detailed further in the review of testicular cancer research, this study only analysed two regions of Great Britain rather than a larger region/country (Toledano et al., 2001). Therefore, this research



project aims to assess the geographical variation of the disease/conditions across a larger region which will be more likely to include sub-regions that differ from each other in terms of several potential risk factors, but not differ in terms of ascertainment.

Finally, if these diseases/conditions are symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS), we would expect to see associations between them. In fact Skakkebaek et al. (2001), recommended that future epidemiological studies on trends in male reproductive health should take into account all aspects of TDS rather than focusing on only one symptom. At present, no such research has been published. Therefore, this research project would appear to be the first analysis of some of the male reproductive health anomalies conjointly, thus addressing another unresolved issue highlighted in previous research.

Therefore the research project aims to provide a complete picture of the spatial variation of three indicators of male reproductive health in Scotland, both by describing the geographical variation and attempting to explain the variation. The research project also aims to address the two main unresolved issues highlighted in previous research, namely the use of consistently collected high quality data for these diseases/conditions data and the conjoint analysis of these indicators.

### **3.3 Spatial Epidemiology Concepts**

This research project is a spatial epidemiological study. Therefore, before explaining the data and the methods used to achieve the study aims the underlying concepts in spatial epidemiology will be introduced in this section. In order to understand why particular methods and data are used these concepts need to be elucidated. Furthermore, how these concepts have implications for the research project are also discussed.

Spatial epidemiology aims to describe and understand the spatial variation of disease. There is a long tradition of the production and analysis of maps within public health research, going back to the 19<sup>th</sup> century (Snow, 1854) . However in recent years the use of this type of study has grown due to the availability and expansion of the

following: geo-referenced health and population data; geographic information systems (G.I.S); computing technology; and statistical methodology.

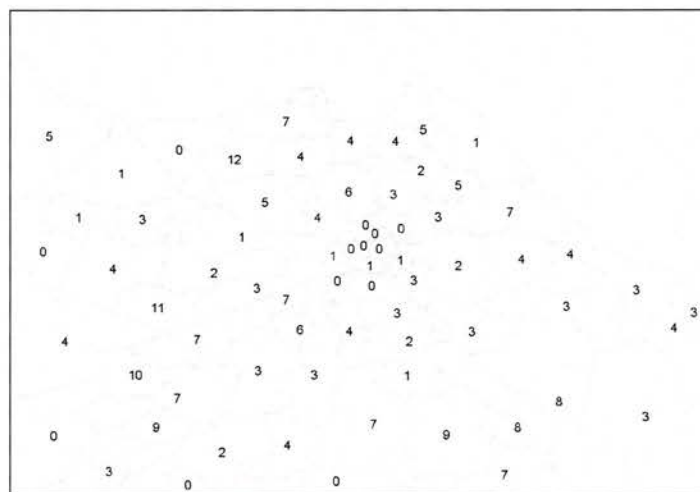
### 3.3.1 Types of Spatial Data

There are two types of geo-referenced data used within spatial epidemiology – **case event** and **count** data. As with any other analysis the type of data available largely determines the particular methodology used, therefore, in order to correctly analyse the data used in the research project we need to identify its type.

For **Case event** data the point location is known for each individual with the particular disease/condition. On a map a case would be presented as a cross or point and the analysis of this type of data would be based on point process models. The datasets within this research project do not contain this level of geographical information. Therefore, further detail on this type of data and the methods used to analyse it are not described.

The datasets used in this research project are count data. Within **count** datasets the point location of cases is not known, but rather in the particular sub-region of the study area in which they are located. Therefore the basis of the analysis is the number of cases of the disease within each of the sub-regions. Figure 4 shows the number of births with cryptorchidism in postcode sectors in Edinburgh from the cryptorchidism dataset within the research project.

**Figure 4 Example of case event data – births with cryptorchidism by postcode sector Edinburgh: 1980-1995**





Increasingly, count data are the only geo-referenced data being made available to researchers carrying out spatial epidemiological studies. Current interpretations of data confidentiality legislation have meant that count data rather than case event data are what are being provided to researchers. The current interpretation is that if the exact location of a case was provided then it might be possible to identify the individual. So the cases geographical information is provided at a higher spatial resolution (i.e. postcode sector in the case of the datasets in this study). More detail on the postcode system in the U.K and its spatial resolution is given in 3.5.

### 3.3.2 Types of spatial epidemiology studies

There are three main types of study in spatial epidemiology, which are largely categorized by the aim of the research:

- (i) **Disease Mapping** aims to illustrate the spatial variation of diseases via the use of maps and is the first type of spatial analysis carried out. These maps, along with corresponding maps of potential explanatory factors, may suggest possible aetiology of the disease in question. The methods used within this type of study have in recent years been developed further with advances in computer technology and the application of Bayesian modelling methods; and these methods have been utilised to address aim (i) of the project.
- (ii) **Disease Clustering** studies aim to determine whether particular regions of a map have a 'cluster' of elevated disease risk. There are two types of disease clustering studies depending on the scale of the analysis and what is defined as a 'cluster'. *Non-focused* clustering analyses look at the whole study region to see if areas within the study region have clustering of sub-regions with higher or lower risks. This is seen as a further refinement of disease mapping and this method is also applied to the first aim of this research project. *Focused* clustering analysis is more specific in the location, structure and number of clusters within a study region. The majority of studies of this type are looking at the effects on health of specific pre-defined putative sources e.g. nuclear power stations, waste dumps, incinerators. This is one of the most well known spatial analysis methods, both within the academic community and among the general public. This is largely because it is associated with



often high-profile potential sources of health hazard. Within this research project this method of analysis is not used, so it is not detailed further.

- (iii) **Ecological analysis** is an extension of disease mapping aiming to assess whether the observed spatial variation of a disease can be explained by other explanatory variables. In ecological analysis the association between disease spatial variation and a possible explanatory variable can be quantified; whereas in disease mapping analysis the maps of the disease and the potential covariates are visually compared to assess if similar in spatial variation. Ecological analysis is used to address the third aim of the research project, to identify explanatory factors that might account for the geographical distribution of the male reproductive health indicators.

Therefore, the analyses undertaken to achieve the three aims of the research project are disease mapping, non-focused clustering and ecological analysis on disease count data.

### 3.3.3 Maps and mapping

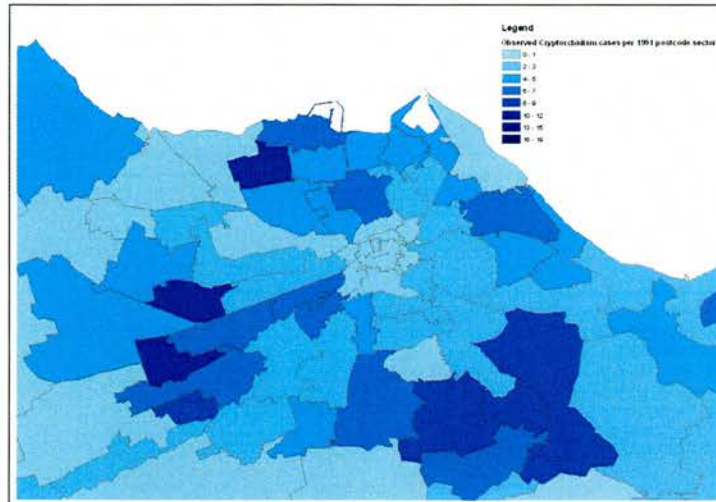
The visual assessment of maps of estimated risks by postcode sectors in Scotland will be an important part of the study. While the maps presented in this research project are as a descriptive/presentation tool, and any inferences made will stem from formal statistical analysis, there are cartographic and visual cognition issues that need to be considered. This section outlines introductory concepts on the use of maps to assess geographical variations of diseases.

It is usual within epidemiology to use *thematic* maps, i.e. colour or shading schemes represent the different relative risks in each sub-region. Figure 5 shows the data from Figure 4 as a thematic map.

The common use of thematic maps within epidemiology is confirmed by cognitive research, which found that epidemiologists prefer thematic maps and used them more accurately than isopleth or dot maps (Pickle *et al.*, 1994). However, the use of thematic maps is not without problems, as the size and pattern of the sub-regions, in this case postcode sectors, will have an impact on any inferences made. Larger postcode sectors tend to draw the viewer's eye towards them even though another smaller postcode sector might have the same category value (Pickle, 2000). Pickle

recommends where possible that the sub-regions should be re-aggregated so that the sub-regions are uniform in size.

**Figure 5** Example of case event data thematic map – births with cryptorchidism by postcode sector Edinburgh: 1980-1995



In Scotland, the postcode sectors areas are certainly not uniform as they are based on population sizes. For instance the North is in the most part rural and so sparsely populated, resulting in postcode sectors with large areas; while the South and particularly the Central Belt is the most densely populated region of Scotland, resulting in postcode sectors with small areas.

Although it would be ideal to re-aggregate, as recommended by Pickle (2000), it was decided to leave the boundaries as they are in this research project. As the data have been provided at the smallest spatial resolution, the re-aggregation to sub-regions of uniform size would result in larger sub-regions. As noted by (Pickle, 2000) aggregation to larger areas are more likely to soak up any variation, particularly if a re-aggregated region contains postcode sectors with widely varying values. Therefore the loss in spatial resolution could result in the potential loss of spatial variation. This would be more likely within Scotland as the re-aggregation would be driven by the largest postcode sectors, which are considerably larger in size than the smallest and less populated.

Therefore, the postcode sectors as the spatial resolution has been retained. In order to reduce the risk of over-emphasis on the larger-in-area postcode sectors, most maps



will also have a close-up of the Central Belt so attention will be directed to the smaller postcode sectors.

The primary use of a map is an important consideration for its production. Bertin classified that there are three basic questions that could be asked using a map (Bertin, 1983). These have been adapted to the conditions of this research project as follows:

- (i) what is the disease risk in a particular postcode sector?
- (ii) are there geographical trends in the relative risks, or clusters of postcode sectors with relatively high or low risks?
- (iii) are the geographical variations of the relative risks different when produced by different Bayesian models?

The aims of the research project mean that the maps produced will either be used to ask (ii) or (iii). For a particular map the question type will determine the style and colours used (Pickle, 2000). For instance, to compare different relative risk maps produced by different Bayesian model for the same disease/condition the categories within the thematic maps will have the same cut-off values.

Finally, the colour schemes used within the thematic maps are also crucial. For cluster recognition, it has been found that one colour gradient is the most effective (Lewandowsky *et al.*, 1993). Blue was chosen as the colour gradient, as the same authors found it had the least ‘value judgement’ associated with it when used in maps. It was decided to use darker shades of blue for the higher values and lighter for the lower, as it has been found that the performance of the map user was better when this ‘convention’ was used (Carswell and Winslow, 1994). The boundaries of the postcode sectors were not given an outline so as to aid in the visual assessment of clustering. Distinct boundaries would over emphasise the difference between postcode sectors which are to a certain extent an artificial construct.

### **3.3.4 Ecological Fallacy**

The use of disease count data may introduce a bias known as ecological fallacy. This is not pertinent to just spatial epidemiology but to epidemiological studies in general where the data being analysed are based on aggregated or grouped data. Ecological bias may occur when an association observed between variables on an aggregated



level does not necessarily represent the association that exists at an individual level. In spatial epidemiology this is taken as inferences made about the spatial variation of the risk between postcode sectors might not translate to the individuals within those postcode sectors.

The potential for this bias to occur is more acute when ecological analysis is carried out. While potential area-specific explanatory variables might explain the spatial variation of a disease it might be that information about the cases in a particular postcode sectors, e.g. age, might explain the geographical variation.

In order to test for the possibility of ecological fallacy in this research project, an individual level analysis of the cryptorchidism cases has been carried out. The methods for this are outlined in 3.7; and aims to see if available information about the individuals has a geographical variation which is similar to that of the geographical variation of the condition's risk and so might explain that variation.

### 3.4 Datasets used within research project

The datasets used in the study can be classified into four categories of data depending on its use within the research project;

- **Male Reproductive Health Disease/Condition** data are the three specific diseases i.e. cryptorchidism, hypospadias and testicular cancer, that are referenced by postcode sector to allow their geographical distributions to be described;
- **Denominator** data are used to standardise, by the underlying population at risk, the number of cases of particular male reproductive health diseases/conditions within postcode sectors;
- **Boundary spatial data** are the geo-referenced border data for Scottish postcode sectors, required to show the geographical distribution of the male reproductive health disease/condition;
- **Potential covariates** are those datasets that will be explored to see if they explain the geographical distributions of the male reproductive health disease/condition data.

As this is a spatial epidemiological study all the data needs to be geo-referenced, in this case by postcode sector – further details on how this is done for each dataset, and further information on the datasets, are given in the subsequent sections. Table 4 summarises all the datasets used in the research project and indicates which of the next sections provides further details on each.

**Table 4      Brief descriptions of datasets used within research project**

Category	Dataset	Source	Further details in section
Male reproductive health disease/condition data	Cryptorchidism	Information Statistics Division (ISD) - maternity/neonatal linked database. (1980-1995)	3.4.1
	Hypospadias		
	Testicular cancer	ISD - linked database (1975-1999)	3.4.2
Denominator data	Birth data	ISD - maternity/neonatal linked database. (1980-1995)	3.4.3.1
	Population data	General Register Office for Scotland (GROS) – Census 1991	None
Boundary spatial data	Postcode Sector boundaries	Census Geography Data Unit (UKBORDERS) – Census 1991 <sup>1</sup>	3.4.4
Potential covariates	Rural/Urban Indicator	General Register Office for Scotland (GROS) – Census 1991	3.4.5.1
	Deprivation	Census 1991 [Carstairs and Norris]	0
	Radon Measurements	National Radiological Protection Board (NRPB) (1980-2000)	3.4.5.3

<sup>1</sup> Digitised Boundary Data (Scotland) Copyright statement – "This work is based on data provided with the support of the ESRC and JISC and uses boundary material which is copyright of the Crown and the Post Office."

The majority of the datasets are freely available either on-line or on request. However, permissions and ethical approvals were required before access was given to the three male reproductive health disease/condition datasets. The Privacy and Advisory Committee (PAC) of the Information Statistics Division (ISD) who collect and provide the datasets, would only give access to the datasets if the spatial resolution was provided only at postcode sector rather than postcode unit level.

As first highlighted in 3.3.1, this was due to current interpretations of data protection legislation, as it is believed that it would be more likely to identify individuals. This interpretation was further confirmed when the ethical approval for the study from the Northern & Yorkshire Multi-Centre Research Ethics Committee (MREC/2/3/40) was given on the same proviso. The postcode system in the UK and the impact of this spatial resolution on the spatial analysis are detailed in 3.5.



### 3.4.1 Cryptorchidism and Hypospadias datasets

The data for both the cryptorchidism and hypospadias cases were extracted from the same database. Therefore, information relevant to this database is outlined first before details on the specific condition data are given.

The database from which these conditions datasets were created is known as the maternity/neonatal linked database from the Information Statistics Division (ISD), which collect and analyse information on NHS activity in Scotland. The maternity/neonatal linked database holds data on maternity (SMR02), neonatal (SMR11) and infant deaths/stillbirths records, and links these records pertaining to a woman and her births. The database includes births from 1980 to 1999 and over this time different data schemes and inclusions have applied. Table 5 shows the different data schemes included in the maternity/neonatal linked database and what would have been included over time.

**Table 5 Overview of data schemes included in maternity/neonatal linked database**

Scheme	Description	Time period
SMR2	All obstetric hospital discharges	1980 – March 1997
COPPISH SMR02	All obstetric hospital discharges	April 1997 – 1999
SMR11	All live births in hospital	1980 – 1991
SMR11 (UV)	All live births in hospital	1992 – March 1996
SMR 11 (EP)	All discharges from SCBU/ITU	1992 – March 1996
COPPISH SMR11	All discharges from SCBU/ITU	April 1996 - 1999

As will be shown the differences in inclusions over time will have an impact on the completeness and quality of the data over time. Firstly, how the data was extracted from the maternity/neonatal linked database is described.

The combined cryptorchidism and hypospadias data file was created using the following selection criteria:

- (i) All SMR2 and SMR11 records from 1980 onwards linked to the same mother (known as patient record set) were selected. All patient record sets containing at least one SMR11 record with a diagnosis of hypospadias or cryptorchidism were selected.
- (ii) A dataset with 8,930 cases was created which contains a baby's record and the corresponding mothers' information. Table 6 shows the frequency within



this dataset of the two conditions. The fields selected from the database are detailed in Appendix 1. These fields were included so as to potentially assess if this information might also explain the spatial variation in the conditions.

**Table 6      Diagnosis frequency in cryptorchidism and hypospadias dataset**

Diagnosis	Number	%
Cryptorchidism	3152	35.3
Hypospadias	5707	63.9
Hypospadias & Cryptorchidism	71	0.8

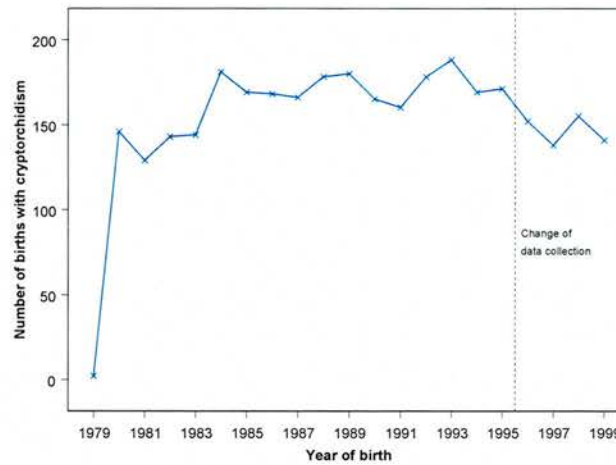
Further notes were supplied with the data extract, and two of these have an impact on the analysis of the data:

- (i) From April 1996 only sick babies generated an SMR11 as can be seen from Table 5. This change in ascertainment is further discussed in relation to each of the two conditions in the next sub-sections.
- (ii) There are 134 babies on the file for which ISD do not have the mother's birth record so do not have information about the mother e.g. age of mother. Therefore analysis of information pertaining to the cases' mother would not be carried out on the complete dataset.

#### **3.4.1.1 Cryptorchidism**

This section outlines how the cryptorchidism cases used in the research project were extracted from the combined cryptorchidism/hypospadias dataset. As can be seen from Table 6 there were 3,223 births with cryptorchidism.

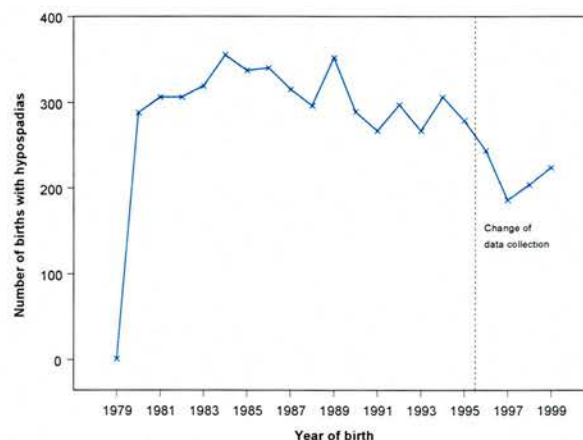
The varying frequency of births with cryptorchidism suggests a need to assess the differences in ascertainment (Figure 6). There are a few cases in the dataset that occurred in 1979. These were probably a run in to the data collection beginning in 1980, so these cases were removed from the dataset as an incomplete year. As already highlighted, from April 1996 only 'sick babies' generated a SMR11 return. It would appear that the numbers of births with cryptorchidism reduced from this time. It might be a true reduction in cases or due to ascertainment. It is likely that cryptorchidism would not be classified as a 'sick baby', so would only be recorded if the baby had further morbidity serious enough to generate a SMR11.

**Figure 6** Cryptorchidism births by year

Therefore it was decided to only include births from 1980 to the end of 1995. The first months of 1996 were also excluded so as to only include complete years. It is likely that there are seasonal differences in the overall births; therefore to avoid introducing potential bias in the numbers of cases only complete years will be included in the data. Therefore the cryptorchidism dataset from which all subsequent analyses will be carried out includes 2,635 cases.

### 3.4.1.2 Hypospadias

As we can see from Table 6 the joint datasets includes 5,778 births with hypospadias. As with the cryptorchidism data there appear to be changes in ascertainment over time (Figure 7).

**Figure 7** Hypospadias births by year

Again there are a few cases that occurred in 1979, and so these were removed from the dataset. The same changes in data collection that applied to cryptorchidism also apply to the hypospadias data, and as can be seen, the number of cases reduced from 1996 onwards. As it is not clear if this is ‘real’ or due to ascertainment, the hypospadias analysis was based on the births between 1980 and 1995, resulting in 4,919 cases.

### **3.4.2 Testicular cancer dataset**

This dataset was also provided by ISD although from another linked database which holds data on non-maternity and non-psychiatric hospital discharges (SMR1), cancer registrations (SMR6), mental health records (SMR4) and death records.

The testicular cancer data file was created using the following selection criteria:

- (i) All cancer registration (SMR6) records where the incidence date is for 1975 to 1999 were selected, as at the time of extraction these were the complete years of registration available.
- (ii) All records containing a diagnosis code for testicular cancer were selected.
- (iii) This resulted in 3,624 records and those fields included in the dataset are shown in Appendix 2. Again these additional fields were requested to potentially investigate if individual covariates explain the spatial variation of testicular cancer.

### **3.4.3 Denominator data**

In order to standardise by the underlying population the number of cases of the three disease/conditions per postcode sector denominator data are required. How these are used is described in 3.6.1, while this section describes the actual data. The denominator used depends on the condition/disease. The population data was used as the denominator data for the testicular cancer data. As detailed in Table 4, the population data is freely available by postcode sector, age and sex from GRO. In order to correspond with the boundary data, the population data was obtained for 1991 Census. However, the birth data had to be requested from ISD, and further details are given here.



### 3.4.3.1 Birth data

The birth data was used as the denominator data for both the cryptorchidism and hypospadias datasets as these were ascertained at birth. It was created from the same maternity/neonatal linked database used to create the cryptorchidism and hypospadias data – see 3.4.1 for more detail. The birth data was created from the linked database by aggregating particular events by postcode sector, year and month. Table 7 shows the events requested from the birth dataset, although only the number of live male births was used as the denominator data.

**Table 7      Events requested from aggregated birth dataset**

Variable
Postcode sector
Year of birth
Month of birth
No. of All Male Births
No. of All Female Births
No. of Live Male Births
No. of Live Female Births
No. of Twins Both Male
No. of Twins Both Female
No. of Twins Both Sexes

### 3.4.4 Boundary data

In order to produce maps of the disease/conditions by postcode sector, one particular time-frame would need to be used, as the postcode sector boundaries change with time. Since the disease/condition datasets span 1975 to 1999 the postcode sector boundary file valid at the 1991 Census was used. It was decided that the boundary files from the Census would be used as they are based on postcode sectors, are widely available, validated and can be cross referenced with population data. Figure 8 shows the boundaries of the postcode sectors as at 1991 Census, and as already mentioned there are differences in sizes of the postcode sectors across Scotland. The postcode sectors are larger in area in the North and South with smaller ones mainly situated in the Central Belt.

**Figure 8** Postcode sector boundaries as at 1991 Census



### **3.4.5 Postcode specific potential covariates**

The third aim of the research project is to identify explanatory factors for the spatial variation of the different disease/conditions. This section outlines the potential covariates used that might explain any geographical variation, while 3.6.3 explains how these will be analysed. While the data of the three disease/conditions contain individual information on the cases there are no postcode sector specific covariates. However, by using the postcode sector we can obtain other postcode specific potential covariates from other datasets. The five postcode specific potential covariates used in this research project are an urban/rural indicator, two deprivation indices and two radon measurements.

Before outlining the potential covariates used in this research project, the process by which these variables were selected needs to be discussed. The spatial variation of the potential covariates is compared to those of the indicators of male reproductive health in order to see if they have similarities. If there appear to be similarities, then it is likely that there is a spatial association between the potential covariate and the particular disease/condition. A more vigorous analysis is to include the potential covariate into the Bayesian spatial models to see if it explains the spatial variation of each of the indicators of male reproductive health, this method is outlined in 3.6.3. For a potential variable to be compared to the spatial variation of the indicators of male reproductive health, it would need to have a spatial component i.e. that its values vary spatially.

A further consideration when selecting potential covariates is that while we will be looking at possible risk factors of male reproductive health to investigate further there are other generic variables which would also need to be considered. As discussed in the review of the human exposure to endocrine disruptors (2.3.2) and summarised in Table 3, the potential risk factors for the manifestation of the various indicators of male reproductive health are numerous and include non-environmental ones. One of the most important of these generic potential risk factors that also varies geographically is deprivation, and two covariates that look at this risk factor have been used and are described in 3.4.5.2.



In terms of possible risk factors of male reproductive health that are specific to the hypothesis that exposure to endocrine disruptors have resulted in these disease/conditions, we need to look at the sources of human exposure to these chemicals as reviewed in 2.3.2 and Table 2, and assess which of these would be suitable to be included in a spatial analysis. As we have seen the primary source of endocrine disruptors for humans is food, which might on first appearance not to be the most appropriate for inclusion as a potential covariate. Food people eat is, in the main, an individually varying covariate rather than a spatially varying one. In recent times, food has generally been transported and consumed away from the area it was produced and so where it was contaminated with the potential endocrine disruptors (e.g. pesticides), and the spatial variation of particular food types (e.g. eggs, meat, grain and vegetables) would be lost. Furthermore, the majority of endocrine disruptors in food are naturally occurring phytoestrogens and the assessment of the level of consumption of these chemicals would chiefly be related to the individual rather than the area they lived.

However, particular chemicals that might enter the food chain may be present in the area in which the food was produced, and so humans could be exposed to these chemicals still present in the area. Therefore spatially varying potential covariates that relate to human exposure of endocrine disruptors via food would stem from the areas where the food was produced. For example, we would wish to obtain levels of particular pesticides across Scotland. Another approach would be to use data that identified if land was used for farming purposes. As pesticides and other endocrine disruptors are used a great deal in this industry, then areas of farming could have correspondingly high levels of these chemicals. As farming is carried out in rural areas, data that can identify between rural and urban areas of Scotland could be a proxy measure. This approach was taken in this research project and the data used are described 3.4.5.1.

Two possible sources of human exposure to endocrine disruptors that are not pursued further in this research project are those found in plastics, pharmaceuticals, cosmetics and other consumer products (e.g. Bisphenol A and phthalates), and those exposed via occupation (e.g. lead, manganese and mercury). As with food consumption, in the

main exposure via these sources would vary by the individual rather than geography, and any available data would be via individual exposure data rather than on a geographical basis.

Two possible sources of human exposure that could be pursued further in this research project are those via water and air.

As described in 2.3.2, exposure to endocrine disruptors via water could either be by residing near contaminated water or by the consumption of such water. For data pertaining to residing near to contaminated sources of water, we require levels of the particular potential chemicals (e.g. hormones, pesticides, PCBs and APEs), with geographical location of where the water sample was taken. It is believed that a more significant source of human exposure via water is by consumption rather than proximity. Therefore if it was possible to obtain water distribution data, i.e. from which reservoir/water source particular areas of Scotland are supplied, then the sample data showing levels of chemicals could be incorporated to potentially give levels of exposure via water consumption.

Industrial pollution and combustion of materials could result in potential endocrine disruptors being present in the air we breathe. Levels of these chemicals (e.g. dioxins and PCBs) in the atmosphere across Scotland could provide the potential exposure of these chemicals via air. Furthermore, reports of incidents of pollution by industrial sites etc., which is a mandatory regulation, could be incorporated to indicate areas where exposure to particular chemicals could have occurred.

While some of the potential data outlined above has been used in this project, some have not been included. Those that were not included are summarised in Table 8 and the reasons why have also been outlined.

Ideally the potential covariate data would be available at the same resolution as the disease data, so as to make direct comparisons. If this was not the case, the next possibility would be that the data could be converted into comparable data. This was not always possible and so certain possible sources of exposure were not included. As with any project there is a balance between time available and what can be done in that time, and so the conversion of potential covariate data to correspond with the



disease data would not always have been practical. Furthermore the lack of availability to this researcher of particular potential covariates also impeded the inclusion of some data. For example, water distribution data, while available, would not be provided to this researcher by either the Scottish Executive or the water companies even following several requests. And while geographically based data might be available interactively via the internet, the underlying datasets needed for the analysis, would not be provided.

**Table 8 Potential Covariates not included in research project**

Potential Covariate	Description of Data found	Reasons for not including
Pesticides	Incidence of poisoning (by chemical) of wildlife/animals by year and region	Regions could not be directly mapped to postcode sector
Land use/ livestock types	Annual classification of land use by agricultural regions	Agricultural regions could not be directly mapped to postcode sector, and refused data at spatial resolution that would have corresponded.
Water Pollution	Samples across Scotland taken annually from range of water systems, chemical levels identified	Data available interactively via website by particular chemicals, year or location able select sample but not able to download or obtain complete dataset
Water distribution	Areas served by particular reservoirs etc.	Unable to obtain from water companies or Scottish Executive
Air pollution	Point data of specific sites of pollution (e.g. industries) and levels of chemicals	Data available interactively via website by particular chemicals, year or location able select sample but not able to download or obtain complete dataset

Therefore the geographically based environmental data available to this researcher was limited. So as to show, if available, how environmental data could be used in the spatial models, radon data was included and is described in 3.4.5.3. A discussion of what environmental data could be included if time and logistics permitted, and the limitations of those used, are given in 8.3.1 and 8.2.1.5 respectively.

### **3.4.5.1 Rural/urban indicator**

As discussed, it is hypothesised that the decline in male reproductive health is due to increasing exposure to environmental oestrogens and one of the potential sources is large scale pesticide use. As large scale pesticide use is a result of farming it could be assumed that farming areas would have higher rates of these conditions. A proxy for assessing if sub-regions are farming areas is the rural/urban indicator from the 1991 Census. This indicator is based on the population within postcode sectors as at the



1991 Census. The frequencies of the five groups of the rural/urban indicator in the 895 postcode sectors in Scotland in 1991 Census are shown in Table 9.

**Table 9 Rural/Urban indicator postcode sector frequency**

Rural/Urban Indicator Code	Population	Number of postcode sectors (%)
1	$\geq 1,000,000$	160 (17.9)
2	100,000 – 999,999	140 (15.6)
3	10,000 – 99,999	203 (22.7)
4	1,000 – 9,999	205 (23.0)
5	<1,000	187 (20.9)

The spatial distribution of the rural/urban indicator within the postcode sectors is shown in Figure 9. As would be expected there appears to be spatial clustering of these indicators; most of the rural areas are grouped in the West and North while the urban areas are in the Central Belt.

#### **3.4.5.2 Deprivation indices**

Deprivation is associated with several health indicators (Carstairs, 1995), and so could have association with these anomalies of male reproductive health. Based on 1991 census information deprivation indices were developed (Carstairs and Morris, 1990). The indices are based on a combination of 4 socio-economic indicators from the census – the percentage of people in an area; without a car; in overcrowded housing; with head of household in social class IV or V; and men unemployed. The spatial distributions of the two groupings used are shown in Figure 10 (quintiles of Carstairs score) and Figure 11 (septiles) within the 895 postcode sectors in Scotland as at 1991 Census.

**Figure 9 Rural/Urban Indicator from 1991 Census population: Scotland and Central Belt**

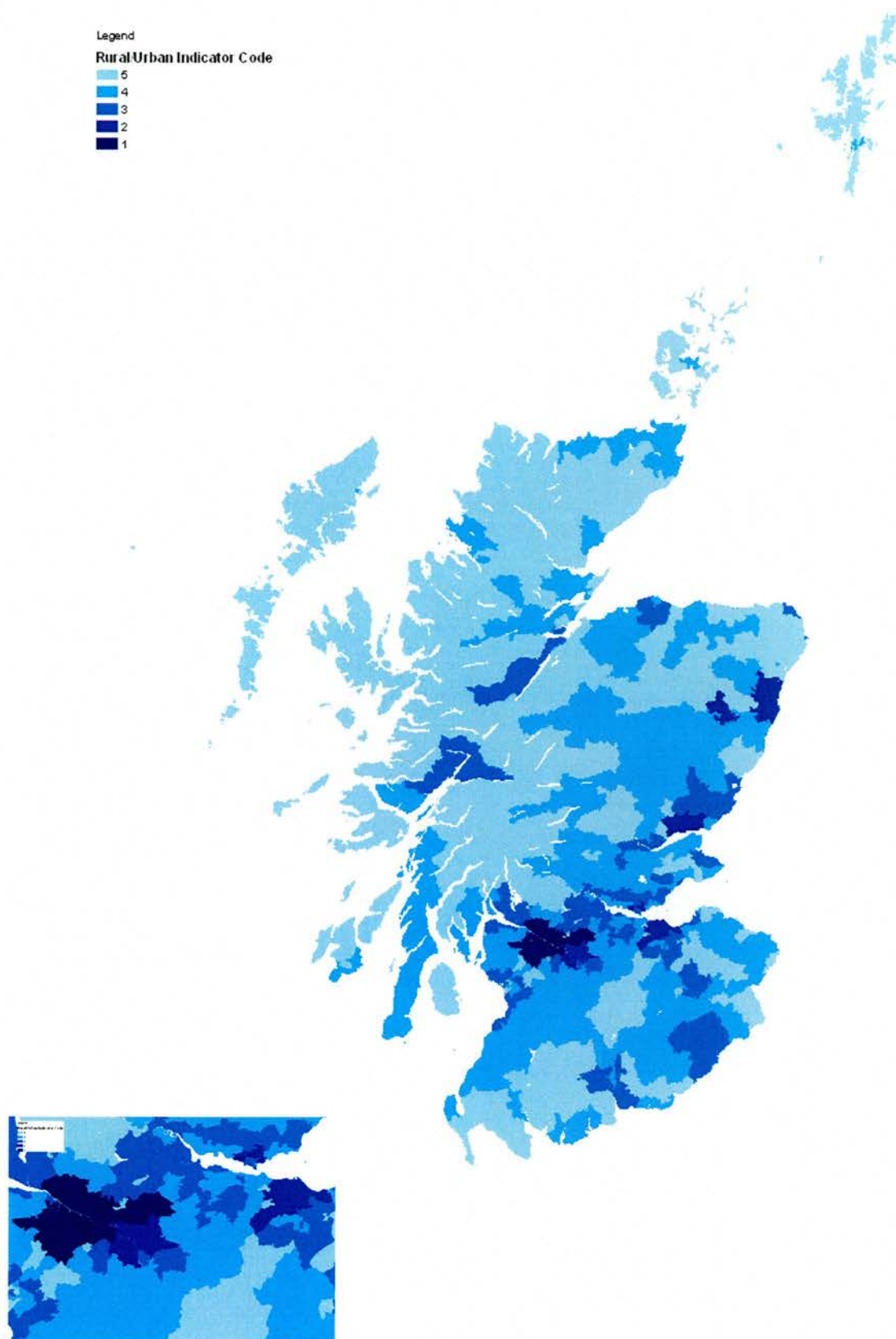


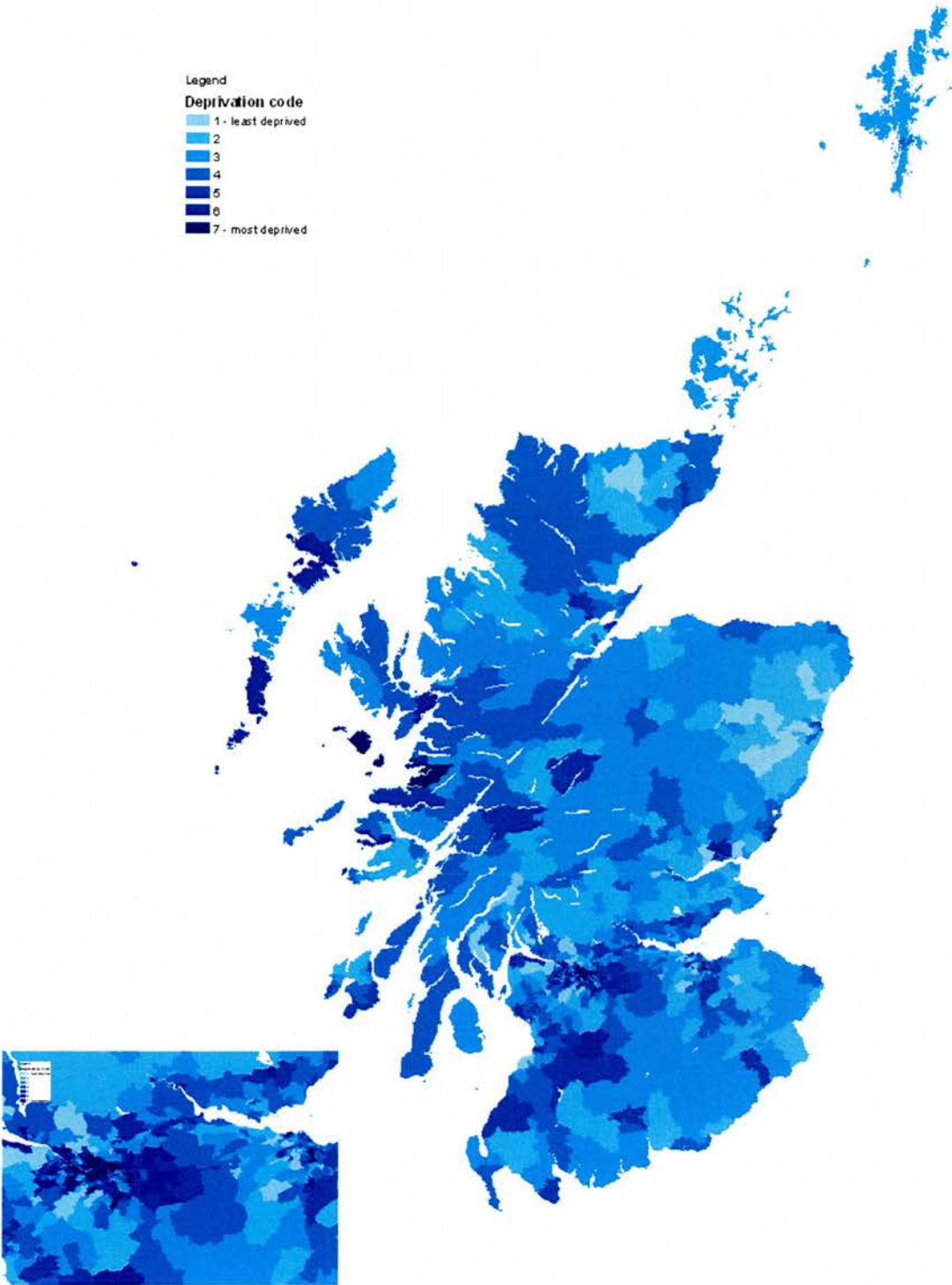
Figure 10 Deprivation Code (5 groups) from 1991 Census: Scotland and Central Belt





There appears to be some clustering of both of the deprivation codes, low deprivation in the North and North-East and high deprivation in the West, South West and the conurbations of the Central Belt.

**Figure 11    Deprivation Code (7 groups) from 1991 Census: Scotland and Central Belt**



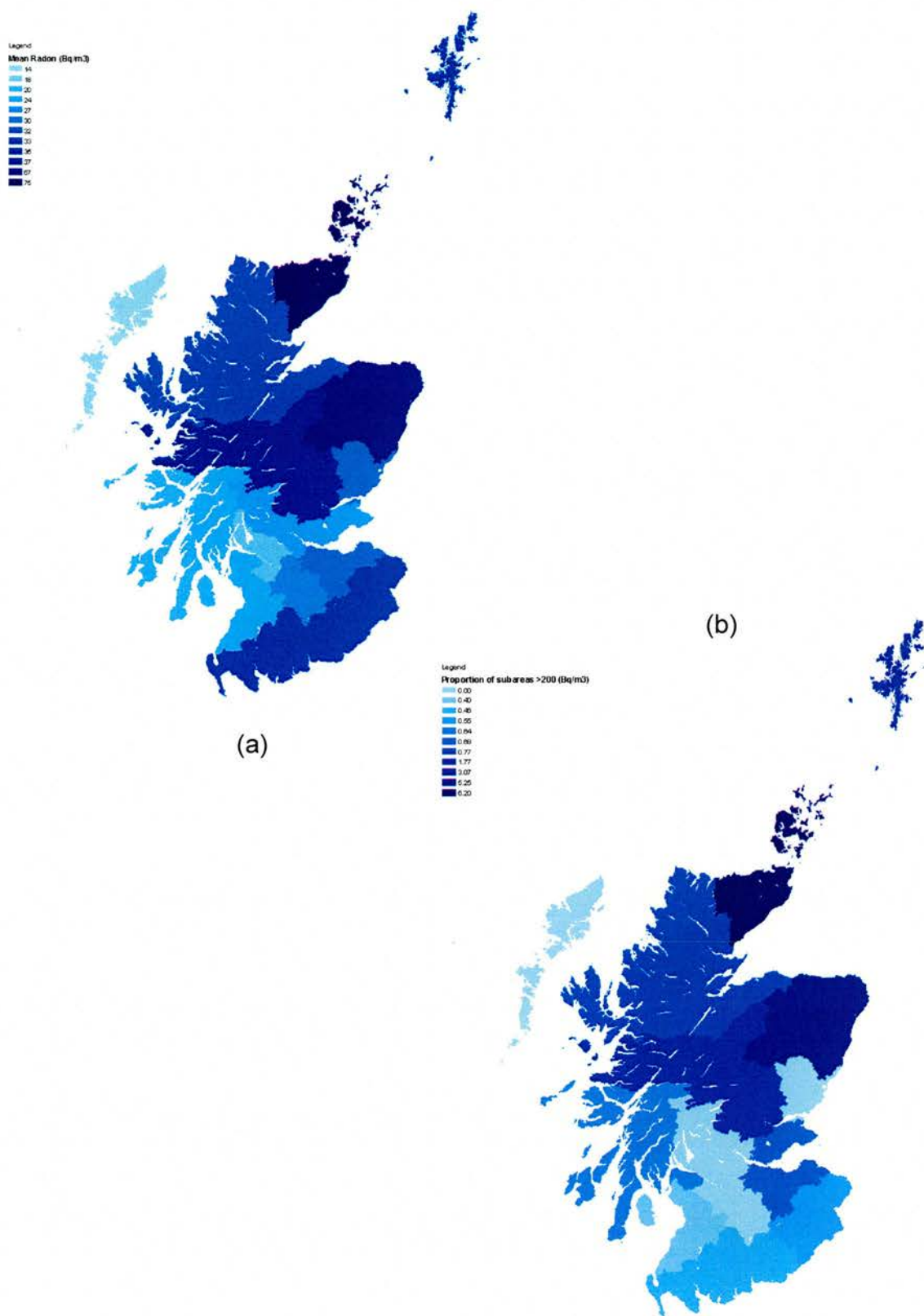
### **3.4.5.3 Radon measurements**

There are particular areas of the UK that have higher levels of radon exposure, one of which is north-east Scotland. Some health conditions have been associated with excessive exposure e.g. lung cancer (Bilello, Murin, and Matthey, 2002). While radon has not been associated with male reproductive health it is a potential environmental pollutant that might also impact on these anomalies. An estimated 84% of the exposure of the population to radiation comes from natural sources, with radon being the greatest source (NRPB, 2003).

The radon data are currently not available at postcode sector level. The results are aggregated to the first two letters of the postcode, although several measurements have been carried out in the area, e.g. 'AB' known as a postcode area. There are two measures of radon which will be assessed. Firstly, the mean radon level  $\text{Bq/m}^3$  within each postcode area. Secondly, the proportion of measurements taken within a postcode area that exceed  $200 \text{ Bq/m}^3$ , the recommended action level for radon in the home according to the National Radiological Protection Board (NRPB). Figure 12 shows the spatial distribution of these two measurements.

Each value has been given an individual colour so as to differentiate between areas, as it must be remembered that the postcode areas are much larger than postcode sectors. With this in mind, there does appear to be a pattern to the two measurements. For the mean radon measurements (a) there appears to be high radon values in the North, North-East and South with lower values in the Central Belt. For the excess radon (b) there is a slightly different pattern. While the North and North-East have higher proportions of areas with excess radon and the Central Belt have lower proportions of areas with excess radon as like the mean radon, the South has lower proportions of areas with excess radon.

**Figure 12** Radon measurements at Region level: Scotland (a) Mean radon (b) Proportion of sub-regions with radon levels exceed 200





### 3.5 Establishing a common geography

As outlined in 3.4, the data are geo-referenced based on postcode sector. The boundaries of these postcode sectors have changed over time. This section describes the postcode system in the UK in more detail; defines the postcode sector within this system and describes how the changes over time have an impact on the production of diseases/conditions maps and how this was resolved for this research project.

#### 3.5.1 Postcode system

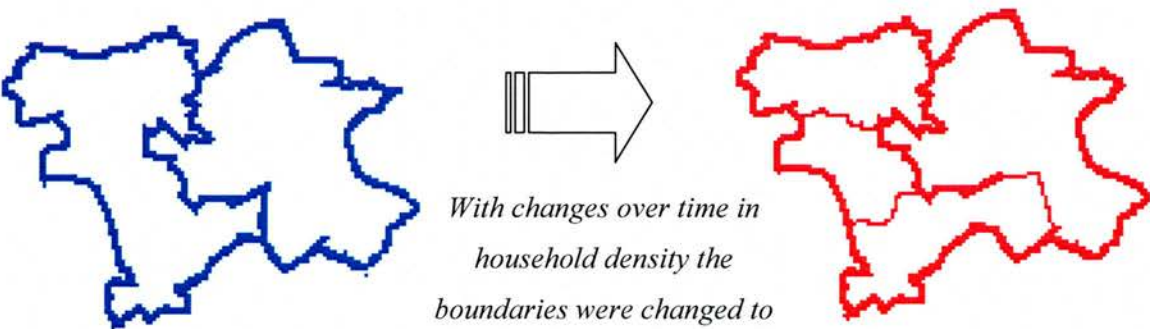
Postcodes were introduced by the Royal Mail so as to provide an accurate and consistent method of delivering mail. It is made up of a combination of letters and numbers which from left to right narrows the destination as illustrated in Table 10.

**Table 10** Postcode system and levels

Postcode level	Example	Description
Postcode Area	EH	Identifies the main Royal Mail sorting office which will process the mail
Postcode District	EH8	Tells the sorting office which delivery office the mail should go to
Postcode Sector	EH8 9	Local area or neighbourhood usually consisting on average of 2,000 households
Postcode Unit	EH8 9AG	Identifies a group of up to 80 addresses and tells the delivery office which postal route (or walk) will deliver the item

As the postcode sectors and units are based on number of households these have to be changed and revised from time to time. For example, a housing development might result in significantly more than 80 addresses in a particular postcode unit or more than 2,000 in a postcode sector, requiring changes in the number of both an area. Figure 13 illustrates these changes in relation to postcode sectors.

**Figure 13** Illustration of postcode sectors changing over time



In the three disease/condition datasets the postcode sector recorded for each case is the postcode sector applicable at the time the case was registered. Therefore a case recorded in the datasets in 1980 might have a postcode sector that does not exist in 1999, and the same addresses within that postcode sector at that time might be in a different postcode sector(s). Therefore the postcode sectors recorded in the datasets are not comparable over time. Furthermore, as already mentioned, in order to produce maps one boundary system needed to be used, which was decided to be that as at 1991 Census.

So in order to undertake spatial analysis and mapping to one boundary system it is necessary to re-assign all postcode sectors to the 1991 postcode sector boundary system.

### **3.5.2 Methods used to re-assign postcode sectors**

Once the changes in postcode sectors were understood to impact on the spatial analysis and mapping of the different disease/conditions, it was assumed that information to match postcode sectors over time would be widely available. This is a common requirement as previous disease maps have been produced from data spanning a number of years.

The majority of previous spatial analyses were provided with the postcode unit rather than postcode sector. Therefore the centre point (centroid) of the postcode unit could be overlaid with the boundary system and so accurately locate in which postcode sector a postcode unit would be. However as already discussed, due to changes in data protection interpretations only postcode sector was provided for the disease/condition datasets, therefore this solution could not be used; and no solution was found for matching postcode sectors over time.

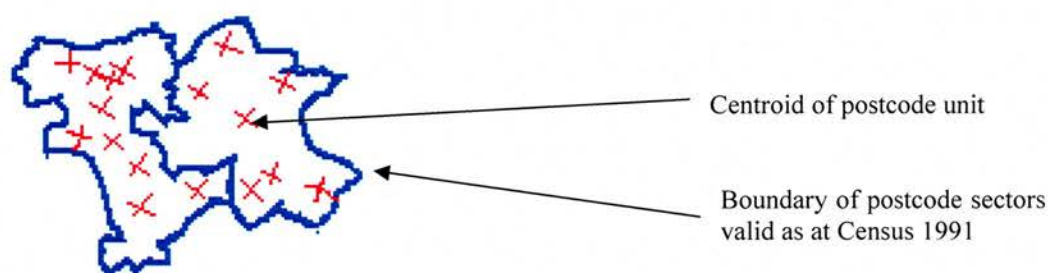
Matching postcode sectors to those postcode sector boundaries valid as at 1991 is not straightforward due to the nature of the changing of boundaries. As we can see in Figure 13 a new postcode sector might not directly overlay a previous postcode sector i.e. be made of sections of more than one old postcode sector. However, the linking of postcode units to a postcode sector boundary system, introduced in the



previous paragraph, could be used as a basis to assign postcode sectors to those valid as at 1991.

Firstly, the centroids of all the postcode units ever used are overlaid with the postcode sector boundaries as at 1991 within a geographical information system (in this case ArcView), as shown in Figure 14. The centroids of all the postcode units ever used were provided from the ‘All Fields Postcode Directory’ from the Office for National Statistics. It contained 179,868 postcode units for Scotland, for which 179,662 (99.9%) had centroid co-ordinates.

**Figure 14** Illustration of spatial linkage of all postcode units to postcode sectors valid as at 1991 Census



This meant it was possible to spatially link every postcode unit ever used in Scotland to the postcode sector they would have been located in as at 1991. As the postcode sectors over time are required it was then necessary to aggregate the postcode units to postcode sector level. This then produced a file for every postcode sector ever used matched to a 1991 postcode sector.

In this file there are some of the postcode units that link to more than one 1991 postcode sector. This can happen for instance when a postcode sector splits into more than one new postcode sector. When this occurred, the 1991 postcode sector to which the majority of the postcode units are linked is used as the match.

Therefore a file was created that was able to match postcode sectors to one common geography – postcode sectors as at 1991 – and appears to be the first complete file produced. There are other files that have looked at this issue within Scotland, however, each is for their own local needs and have their own particular problems. Public Health Institute of Scotland (PHIS) – has produced a file that tracks census



tracts from one Census to another. These census tracts are similar to postcode sectors in Scotland but do alter in a number of areas. Furthermore the file was created to proportionally assign populations to census tracts over time rather than match particular census tracts; therefore there is no one-to-one match.

ISD and GROS have developed a file that provides a one-to-one match of postcode sectors to the postcode sectors valid at the 1991 census. However, this information was developed on a piece-meal fashion based on local knowledge rather than a systematic linkage across Scotland.

Although the file used in the research project appears to be the first of its kind, the methods used do have limitations that need to be discussed. The use of centroid of the postcode units to link to those postcode sectors valid as at 1991 assumes that the spatial distribution of the population within the units are uniform. This might not be the case e.g. the north part of a postcode unit might be more densely populated than the south, meaning that an individual could be assigned to a neighbouring postcode sector incorrectly. However, as the postcode units are at a small spatial resolution the effect should be minimal. Furthermore, as the assignment to a 1991 postcode sector is based on where do the majority of the postcode units lie then this type of mis-assignment is less likely.

But the assignment to 1991 postcode sectors based on the majority of postcode units will have meant that some postcode sectors have been assigned to neighbouring postcode sectors. However this mis-assignment is small. Of the 179,662 postcode units 6,580 (3.7%) were found to be in one 1991 postcode sector but were assigned to its neighbour as the majority of the other postcode units were within that sector. Furthermore, it must be remembered that the spatial analysis is interested in the general spatial distribution of the diseases rather than the particular numbers within postcode sectors, so the small chance of mis-assignment is unlikely to impact on the overall aim of the analysis.

It might have also been possible to proportionally assign cases aggregated to postcode sector to the 1991 postcode sectors. As particular postcode units aggregated to postcode sector linked to more than one 1991 postcode sector we could have used

the proportions of postcode units as a proportion to assign aggregated diseases cases. However, this would have meant the loss of individual level information related to the case as it would have not been possible to attach a postcode sector to each case. And as we do have individual level information for each case, that might explain spatial variation in the disease risk, we would not want to lose this level of information.

With the disease/condition cases assigned to one common geography i.e. postcode sector valid as at the 1991 Census, it would be now be possible to look at the spatial variation of the different diseases/conditions.

### **3.6 Analysis of disease/conditions count data**

This section summarises the methods used to describe the geographical variation of the three disease/conditions as counts of cases per 1991 postcode sector. Each subsection is a progression of the previous as the methods are developed.

#### **3.6.1 Standard Morbidity Ratio (SMR) maps**

Maps of the Standard Morbidity Ratios (SMRs) have long been used to look at the geographical variation on a particular diseases/conditions or condition. Maps of the number of cases within each postcode sector can result in misleading inferences, as these values do not take account of the spatial variation in the underlying population at risk. However, the SMR takes the size of the population at risk into account within each postcode sector. The SMR is the maximum likelihood estimate (MLE) of the relative risk for each postcode sector and is calculated as follows:

$$\text{SMR} = \frac{\text{observed number of cases of disease in 1991 postcode sector}}{\text{expected number of cases of disease in 1991 postcode sector}}$$

The postcode sector of all cases in each of the disease/conditions datasets were re-assigned to the 1991 postcode sectors using the methods described in section 3.5. Summing these cases by the 1991 postcode sector gives the observed number of cases.

The expected number of cases within each of 1991 postcode sectors involves calculating national rates for each disease/condition which are then applied to the underlying population at risk, as follows:



Firstly, calculate national rates for a disease/condition by standardisation category:

Standardisation category	Population at risk in standardisation category	Number of cases of diseases/conditions in standardisation category		National Rates of disease/condition by standardisation category
$C_1$	$P_1$	$D_1$	=	$D_1 / P_1$
$C_2$	$P_2$	$D_2$	=	$D_2 / P_2$
...				
$C_n$	$P_n$	$D_n$	=	$D_n / P_n$

Then these national rates are applied by standardised category to the underlying population within each postcode sector to calculate the expected number of diseases/conditions cases as follows:

For 1991 postcode sector j:

Population at risk in $C_1$ and 1991 postcode sector j	x	$D_1 / P_1$	=	$e_{1j}$
Population at risk in $C_2$ and 1991 postcode sector j	x	$D_2 / P_2$	=	$e_{2j}$
...				
Population at risk in $C_n$ and 1991 postcode sector j	x	$D_n / P_n$	=	$e_{18j}$
<b>Expected number of diseases/conditions cases in postcode sector j</b>				$\sum e$

Although the method is the same irrespective of disease/condition the population at risk and the standardisation category are different for each. Table 11 shows those used for each of the diseases/conditions to calculate the expected rates per 1991 postcode sector. Details on the Population at Risk datasets have been given earlier – known as denominator data.

**Table 11    Population at Risk and Standardisation Categories used to calculate expected rates per postcode sector for each disease/condition**

Disease/Condition	Population at Risk	Standardisation category
Cryptorchidism	All births – maternity/neonatal linked database, ISD	Year of birth
Hypospadias	All births – maternity/neonatal linked database, ISD	Year of birth
Testicular cancer	Population – Census 1991	Age groups

Although the SMRs maps have long been used in spatial epidemiology to show the spatial variation of a disease and do take into account the spatial variation of the underlying population, they have a number of shortcomings, particularly when carried out on areas with small number of cases.



As the SMR is based on the ratio of observed and expected values per postcode sector, any variation in the disease risk would be dominated by the uncertainty of the estimates, particularly in areas with small number of cases. In order to see the variability of the SMRs, the maps of the standard errors of these estimates are compared to the actual SMR maps. If the standard errors of the SMRs show a similar spatial variation as the SMRs then it is likely there are dominated by the uncertainty of the estimates.

The standard error of the SMR for each postcode sector is calculated as:

$$\text{Standard error (SMR)} = \frac{\sqrt{\text{observed number of cases of disease in 1991 postcode sector}}}{\text{expected number of cases of disease in 1991 postcode sector}}$$

In order to account for the variability of the relative risk estimates, that might either be random or spatially structured, Bayesian Hierarchical modelling is required.

### **3.6.2 Bayesian Hierarchical Modelling of disease/condition count data**

In general Bayesian hierarchical models attempt to remove the random variation or random effects of the relative risk estimates from the map. Modelling random effects attempt to quantify unobserved effects within a model. How this is done depends on the assumptions made within each model and on the nature of the random effects.

This section outlines the three different Bayesian models used with the three disease/condition datasets. Each model make different assumptions about the spatial variation of the relative risks and have been used with all three disease/condition datasets to assess which best describes the geographical variation of the diseases/conditions and so give a better insight into their spatial variation. For each disease/condition the posterior estimates and the resulting maps from each of the three models were compared to see which terms best describe the spatial distribution of each disease.

In order to understand the models an introduction to Bayesian modelling is required.

### 3.6.2.1 Bayesian Theory

As noted by (Congdon, 2001), the general principle of Bayesian analysis is that prior knowledge about the density of the parameters within a model are combined with either sample data or previous experimental evidence to produce updated knowledge about the parameters. Within a spatial Bayesian modeling context this translates as the crude relative risks (i.e. SMRs) being combined with models that make assumptions about the spatial variation of these risks to produce new estimates of the relative risks which take into account the variability of the estimates.

In general, if we have data  $\{y_i\}$  with parameters  $\{\theta_i\}$  then its *likelihood* is denoted as  $L(\mathbf{y}|\boldsymbol{\theta})$  and the log-likelihood as  $l(\mathbf{y}|\boldsymbol{\theta})$ . The prior knowledge concerning the parameters are assumed to have distributions known as *prior* distributions represented as  $g(\theta_i)$ , where the joint distribution of the parameters is  $\mathbf{g}(\boldsymbol{\theta})$ . The distributions of the updated parameters produced by taking into account the prior distributions are known as the *posterior* distributions, and are the product of the likelihood and the prior. So, if the posterior distributions is represented by  $p(\boldsymbol{\theta}|\mathbf{y})$ , then,

$$p(\boldsymbol{\theta}|\mathbf{y}) \propto L(\mathbf{y}|\boldsymbol{\theta}) \mathbf{g}(\boldsymbol{\theta})$$

It is impossible to produce point estimates for the updated parameters from Bayesian models as it assumed that the parameters occur from a distribution of possible values. For simple models it is possible to find the exact form of the posterior distribution and so any summaries of interest. However, for most realistic hierarchical models, unless the posterior produced is of a closed form, it is not possible to find the exact form. Classic estimation methods were used to estimate the maximum likelihood estimates of the posterior for the parameter of interest e.g. the Newton-Raphson and least squares methods. However they were impractical with large numbers of parameters and only with very simple hierarchical models. Therefore the use of Bayesian analysis was limited in its scope for a number of years due to the constraints of producing estimates of the posterior distributions.

However with the introduction of higher performance computers, simulation methods could be developed to estimate the entire posterior distribution of the parameters. Samples could be taken from the posterior density, which could then be



summarised to produce estimates of interest. Markov Chain Monte Carlo (MCMC) based methods were used which simulated parameter values iteratively within a Markov Chain. A number of MCMC based algorithms were developed to perform these iterations: Metropolis updates, Metropolis-Hastings updates and Gibbs updates. The most used of these algorithms within epidemiology is the Gibbs algorithms, as it is the basis of the widely used Bayesian analysis packages MLwiN and the package used for this research project WinBUGs. More information on the use of WinBUGs in this research project can be found in 3.9.

### **3.6.2.2 Poisson-Gamma model**

The first Bayesian hierarchical model used in the analysis, known as the Poisson-Gamma model, is one of the first to have been used in spatial epidemiology.

If we denote the observed number of cases of a disease in 1991 postcode sector  $i$  as  $y_i$ , and the expected number of cases as  $e_i$ . Then the SMR for 1991 postcode sector  $i$ , which is the MLE estimate of the relative risk  $\hat{\theta}_i$  is

$$\hat{\theta}_i = \frac{y_i}{e_i}$$

The binomial distribution typically applies when counting the number of cases of an event occurring or not. However, within these datasets and with other epidemiological data the key interest is the number of times when a disease occurs, and do not know when it does not occur. In such a situation, and when the event is rare, the Poisson distribution is a good approximate of the binomial. Therefore, if we assume that the numbers of cases of a disease within each postcode sector are independent then

$$y_i \sim \text{Poisson}(e_i \theta_i) \quad \forall i$$

A Gamma prior distribution for the crude relative risks combines conveniently with the Poisson likelihood for the number of cases to give a gamma posterior distribution for the estimates of the relative risks. Those postcode sectors with SMRs with high variance will have a posterior mean relative risk smoothed towards the global mean relative risk, while those with a small variance will have a posterior mean relative risk close to the SMR.



The WinBUGs code for the Poisson-Gamma model used for the three diseases/conditions is shown in Figure 15. As a result of the posterior relative risks having a gamma distribution  $\text{Gamma}(a, b)$  then the overall mean relative risk is  $a/b$ . For a full Bayesian model these hyper-parameters  $a$  and  $b$  are also given prior distributions. For these datasets an exponential distribution of mean 1 was given for  $a$  and a gamma distribution with shape parameter 0.1 and scale parameter 1 was given for  $b$ .

**Figure 15 WinBUGs code for Poisson-Gamma model**

```
model
{
  for(i in 1:m)
  {
    # Poisson likelihood for observed counts
    y[i]~dpois(mu[i])
    mu[i]<-e[i]*theta[i]
    # Relative Risk
    theta[i]~dgamma(a,b)
    #Posterior probability of theta>1
    PP[i]<-step(theta[i]-1+eps)
  }
  eps<-1.0E-6
  #Prior distributions for parameters
  a~dexp(1)
  b~dgamma(0.1,1.0)
  # Population mean and variance
  mean<-a/b
  var<-a/pow(b,2)}
```

It is possible to give these hyper-parameters different priors, and in fact it is recommended to undertake a sensitivity analysis of any Bayesian hierarchical models by comparing posterior estimates from models with different hyper-parameters priors (O'Hagan, 2003). However, the aim of the analysis is large scale disease mapping i.e. looking at large-scale spatial variation rather than specific relative risk estimates and it was not practical in terms of time to carry out this level of analysis on all the Bayesian hierarchical models described. It was therefore decided to carry out sensitivity analysis only on the Besag, York and Mollié (BYM) model for each disease/condition. How this was done and why is described in 3.6.2.4. However, all priors specified have been taken from WinBUGs examples in either textbooks (Lawson, Browne, and Vidal Rodeiro, 2003; Congdon, 2001) or the WinBUGs manual.

Also included in the WinBUGs code is the calculation of posterior probabilities of the relative risk being greater than 1. A map of these values will show the probability that the posterior relative risk within each postcode sector is greater than 1. This value gives an indication of which areas have a higher disease risk, while accounting for the variability of the relative risk estimate. All the Bayesian hierarchical disease count models will include this calculation and subsequent maps.

The Poisson-Gamma model smooths the posterior relative risks towards the overall mean relative risk, and so decreases the range of their values and variability. However, it does not account for spatial correlation i.e. that a postcode sector will be similar to its neighbours. Furthermore, the inclusion of other covariates is not possible within a Poisson-Gamma model.

### **3.6.2.3 Log-Normal model**

A more flexible model which could include other covariates was then developed (Clayton and Kaldor, 1987). This model known as the Log-normal model, again assumes a Poisson likelihood for the observed number of diseases/conditions per 1991 postcode sector. However, rather than gamma priors for the crude relative risks this model uses a normal prior distribution on the logarithm of the relative risk

$$\begin{aligned} \text{i.e.} \quad y_i &\sim \text{Poisson}(e_i \mathcal{G}_i), \\ \log \mathcal{G}_i &= \alpha + v_i, \\ v_i &\sim N(0, \tau_v^2) \end{aligned}$$

Therefore unlike the Poisson-Gamma model, the Log-Normal model can include covariate information. However as with the Poisson-Gamma model it includes a component that assumes that the random effects vary between areas in an unstructured way, known as uncorrelated heterogeneity  $v_i$ . Uncorrelated heterogeneity assumes that within the model that any extra variation is not correlated with the location of the disease, i.e. the location of any clustering of diseases is a random effect. Therefore the SMRs are smoothed towards the overall mean relative risk, where  $\alpha$  represents the overall relative risk within the model. Figure 16 shows the WinBUGs code for the Log-Normal model which was used on the three

disease/condition datasets. As with the Poisson-Gamma model the same priors for the hyper-parameters were used for each disease dataset, for the same reasons given in 3.6.2.2.

**Figure 16 WinBUGs code for Log-Normal model**

```
model
{
  for (i in 1:m)
  {
    #Poisson likelihood for observed counts
    y[i]~dpois(mu[i])
    log(mu[i])<-log(e[i])+alpha+v[i]
    #Relative Risk
    theta[i]<-exp(alpha+v[i])
    #Posterior probability of theta>1
    PP[i]<-step(theta[i]-1+eps)
    #Prior distribution for the uncorrelated heterogeneity
    v[i]~dnorm(0,tau.v)
  }
  eps<-1.0E-6
  #Vague distribution for the mean relative risk in the study region
  alpha~dflat()
  mean<-exp(alpha)
  #Hyperprior distributions on inverse variance parameters of random effects
  tau.v~dgamma(0.5,0.0005)}
```

### 3.6.2.4 Besag, York and Mollié (BYM) model

As already mentioned both the Poisson-Gamma and the Log-Normal models do not take into account that there might be spatial correlation in the relative risks. Spatial correlation is the assumption that the relative risk value of a postcode sector would tend to be similar to the neighbouring postcode sectors.

An extension to the Log-normal model that also included a spatially correlated heterogeneity term was first introduced in 1987 (Clayton and Kaldor, 1987) and was further developed in 1991 (Besag, York, and Mollie, 1991) and will be referred to as the Besag, York and Mollié (BYM) model. This spatially correlated heterogeneity term assumes that there is a correlation between any extra variation and the spatial unit (in this case postcode sector) and its neighbours. This could be because the disease is naturally clustered or brought about because of unobserved effects. Therefore the estimation of the relative risk for each postcode sector will depend on the neighbouring postcode sectors.



So, as with the log-normal model

$$y_i \sim \text{Poisson}(e_i \mathcal{G}_i),$$

$$\text{but,} \quad \log \mathcal{G}_i = \alpha + u_i + v_i,$$

where, as with the Log-normal model,  $\alpha$  represents the overall relative risk and  $v_i$  is the uncorrelated heterogeneity which has the same normal prior. For the spatial correlated heterogeneity term  $u_i$ , Besag, York and Mollié proposed that a conditional autoregressive models (CAR) prior was specified (Besag, York, and Mollie, 1991). As detailed by Lawson, Browne, and Vidal Rodeiro (Lawson, Browne, and Vidal Rodeiro, 2003) this is

$$[u_i | u_j, i \neq j, \tau_i^2] \sim N(\bar{u}_i, \tau_i^2)$$

$$\text{where} \quad \bar{u}_i = \frac{1}{\sum_j \omega_{ij}} \sum_j u_j \omega_{ij},$$

$$\text{and} \quad \tau_i^2 = \frac{\tau_u^2}{\sum_j \omega_{ij}},$$

$$\omega_{ij} = 1, \text{ if } i, j \text{ are neighbours (0 if they are not).}$$

So the distribution of the log relative risk in postcode sector  $i$  is normal with mean given by the mean of the log of the relative risks in the neighbouring postcode sectors and the variance being proportional to the number of neighbouring postcode sectors.

Figure 17 shows the implementation of the BYM model in WinBUGs as suggested by Lawson, Browne, and Vidal Rodeiro (2003). This is similar to the WinBUGs code for the Log-normal model but with an additional spatial correlated heterogeneity term. The CAR model proposed by Besag, York and Mollié (1991) is available from GeoBUGs, an add-on spatial module of WinBUGs, via the `car.normal` distribution and requires the following terms to be specified:

- (i) `adj[]` is a vector containing the adjacent postcode sectors for each postcode sector

- (ii) `weights[]` is a vector containing weights associated with each pair of postcode sectors – within this model the weights are 1 for all pairs
- (iii) `num[]` contains the number of neighbours for each postcode sector
- (iv) `tau.u` represents the inverse-variance of the spatial correlated heterogeneity.

While `tau.u` is assigned a prior gamma distribution, the other terms are specified and so have to be added as data. Within GeoBUGs these terms can be generated by the Adjacency Tool using the 1991 postcode sector boundary file.

**Figure 17 WinBUGs code for BYM model**

```
model
{
  for (i in 1:m)
  {
    #Poisson likelihood for observed counts
    y[i]~dpois(mu[i])
    log(mu[i])<-log(e[i])+alpha+u[i]+v[i]
    #Relative Risk
    theta[i]<-exp(alpha+u[i]+v[i])
    #Posterior probability of theta>1
    PP[i]<-step(theta[i]-1+eps)
    #Prior distribution for the uncorrelated heterogeneity
    v[i]~dnorm(0,tau.v)
  }
  eps<-1.0E-6
  #CAR distribution for the spatial correlated heterogeneity
  u[1:m]~car.normal(adj[], weights[], num[], tau.u)
  #Weights
  for (k in 1:sumNumNeigh)
  {
    weights[k]<-1
  }
  #Vague distribution for the mean relative risk in the study region
  alpha~dflat()
  mean<-exp(alpha)
  #Hyperprior distributions on inverse variance parameters of random effects
  tau.u~dgamma(1,1)
  tau.v~dgamma(0.5,0.0005)}
```

As previously discussed in relation to the Poisson-Gamma and Log-Normal models, sensitivity analysis is recommended so as to assess the performance of the hyper-priors specified. Unlike the two other Bayesian models it was decided to carry out sensitivity analysis on the inverse-variance of the spatial correlated heterogeneity (`tau.u`), because as will be seen in Chapters 4, 5 and 6 there were concerns that the spatially correlated heterogeneity term over-smoothes the relative risk estimates.

The sensitivity analysis was carried out by comparing the relative risks estimated for each postcode sector by the model shown in Figure 17 and by this model with `tau.u` specified as *Gamma*(0.5, 0.0005) which has been suggested for the precision parameter of the spatial random effects in a CAR model (Kelsall and Wakefield,

1999). The comparison of the two sets of relative risks were compared by looking at the correlations and carrying out paired t test to see if there are significant difference between the estimated values. If a significant difference is found then the spatial variation of the two sets of relative risks estimated are compared.

### **3.6.3 Inclusion of covariates into Bayesian Hierarchical models of diseases/conditions count data**

After estimating the spatial variation of the disease risk through the different Bayesian hierarchical disease count models and assessing which best explain the data, the logical next step is to seek to explain the spatial variation. The initial way to accomplish this is to include in the Bayesian hierarchical disease count models, covariates which are postcode sector specific i.e. deprivation, rural/urban indicator and radon.

To see if the spatial distribution of these indicators explains the spatial variation of the cryptorchidism cases we need to include each covariate separately within the BYM and log-normal models. How these covariates are included in the two models is dependent on the nature of the factor.

Both deprivation indices and urban/rural indicator are category variables. Figure 18 (bold) gives an example of the WinBUGs code for the urban/rural indicator being included to the BYM model, and the same coding is used to include all three covariates within the BYM and log-normal models. The covariates are included by eliminating the grand mean and calculating the contrasts between the 5 groups separately.



**Figure 18 WinBUGs code of BYM model plus rural/urban indicator**

```

model
{
  for (i in 1:m)
  {
    #Poisson likelihood for observed counts
    y[i]~dpois(mu[i])
    log(mu[i])<-log(e[i])+alpha+u[i]+v[i]+beta[urban[i]]
    #Relative Risk
    theta[i]<-exp(alpha+u[i]+v[i]+beta[urban[i]])
    #Posterior probability of theta>1
    PP[i]<-step(theta[i]-1+eps)
    #Prior distribution for the uncorrelated heterogeneity
    v[i]~dnorm(0,tau.v)
  }
  eps<-1.0E-6
  #CAR distribution for the spatial correlated heterogeneity
  u[1:m]~car.normal(adj[], weights[], num[], tau.u)
  #Weights
  for (k in 1:sumNumNeigh)
  {
    weights[k]<-1
  }
  #Vague distribution for the mean relative risk in the study region
  alpha~dflat()
  mean<-exp(alpha)
  for (j in 1:5) {
    beta[j] ~ dnorm(0.0, 0.0001)}
    for(j in 2:5) {
      contrast[j-1] <- beta[j]-beta[1]
    }
  }
  #Hyperprior distributions on inverse variance parameters of random effects
  tau.u~dgamma(1,1)
  tau.v~dgamma(1,1)}

```

The two radon measurements are continuous measurements. Figure 19 (bold) shows the WinBUGs code for the inclusion of the mean radon measurement within the BYM model. This is the method used to include both radon measurements within the BYM and log-normal models.

**Figure 19 WinBUGs code of BYM model plus mean radon**

```

model
{
  for (i in 1:m)
  {
    #Poisson likelihood for observed counts
    y[i]~dpois(mu[i])
    log(mu[i])<-log(e[i])+alpha+u[i]+v[i]+beta*radon1[i]
    #Relative Risk
    theta[i]<-exp(alpha+u[i]+v[i]+beta*radon1[i])
    #Posterior probability of theta>1
    PP[i]<-step(theta[i]-1+eps)
    #Prior distribution for the uncorrelated heterogeneity
    v[i]~dnorm(0,tau.v)
  }
  eps<-1.0E-6
  #CAR distribution for the spatial correlated heterogeneity
  u[1:m]~car.normal(adj[], weights[], num[], tau.u)
  #Weights
  for (k in 1:sumNumNeigh)
  {
    weights[k]<-1
  }
  #Vague distribution for the mean relative risk in the study region
  alpha~dflat()
  mean<-exp(alpha)
  beta ~ dnorm(0, 2)
  #Hyperprior distributions on inverse variance parameters of random effects
  tau.u~dgamma(1,1)
  tau.v~dgamma(1,1)}

```

### 3.7 Bayesian Hierarchical Modelling of Individual level data

As discussed earlier (3.3.4), in order to assess the possibility of ecological fallacy, an individual level analysis was to be carried out. An individual analysis would see if information about the cases has a geographical variation similar to that of the geographical variation of the disease risk. If this is the case then it is possible that this individual information explains the geographical variation in the relative risk. However the failure to explain the geographical variation with the individual analysis will not mean that the potential for ecological fallacy is eliminated. Rather that it if is present then it is not due to the information known about the individuals in the datasets.

The individual level analysis described below was carried out only on the cryptorchidism dataset. Ideally, the individual level models would have been carried out on all three disease/conditions and on all the information known about the cases. However, due to time constraints it was decided to use the cryptorchidism datasets as

an example of the potential of such analysis. Furthermore this analysis gives an indication whether information about the individuals might explain the spatial variation in the disease risk rather than geographical based covariates. The results do not give direct associations between disease risk and individual covariates. Development of such models has yet to emerge in this relatively new field of statistical analysis. Therefore the individual analysis was limited in what conclusions could be made from it, consequently it was decided to illustrate the methods with one disease i.e. cryptorchidism; and individual level models were developed for only three key individual level covariates: year of birth, year of mother's birth and co-morbidity.

The year of birth was modelled as will be seen from the cryptorchidism incidence rates in Scotland have increased over time. The age of the mother might explain some spatial variation in cases as previous research proposed that older women might have a higher risk of congenital malformations (Baldwin and Nord, 1984). From the diagnosis fields it was possible to identify which of the cryptorchidism cases were also born with hypospadias. As both these conditions are hypothesised to be caused by the same environmental exposure, these babies may have the same spatial variation as the overall disease risk of cryptorchidism.

### **3.7.1 Models**

The overall approach taken to analyse these three covariates (year of birth, year of mother's birth and co-morbidity) spatially is to regard them as outcome variables. As the individual analysis is within a given population (i.e. cryptorchidism cases) then differentiation is based on the outcome variables and their different levels e.g. year of birth grouping. Then these individual models could include spatial and heterogeneity terms to ascertain the extent to which these effects are required to explain any differences between the groups of individuals.

Unlike the disease count models, we are looking at the locations of individual cases. Therefore the underlying population at risk is not accounted for as was done in the count models. However, if we use polytomous regression models i.e. category based outcomes, the underlying population is controlled within the model. As both the year of birth and age of mother are continuous variables they were converted into



category variables as outlined in Table 12. These categories were selected so that the sub-groups were equal in population size and the number of categories was kept to a minimum.

**Table 12    Conversion of Year of Birth and Mother’s Year of Birth to category variables**

Variable	Categories
Year of Birth	1=1980-1983, 2=1984-1987, 3=1988-1991, 4=1992-1995
Age of Mother (years)	1=14-21, 2=22-29, 3=30-37, 4=38-45

The WinBUGs code for the categorical models for the Year of Birth and Age of Mother are shown in Figure 20. From each model we obtain the probability for each individual of being within each of the categories. The code shows the model with all terms included i.e. coordinates and heterogeneity terms. Each of these terms were added individually to the models to assess which terms best described the variation in probabilities, e.g. does the x co-ordinates of the case location explain the categorisation of the cryptorchidism cases by year of birth.

As there were only two outcomes for the co-morbidity model a logistic regression model was performed i.e. cryptorchidism cases or cryptorchidism and hypospadias cases. As this is a reduction of the polytomous regression model it can also control for the underlying population. The WinBUGs code for the full model is shown in Figure 21 which produces the probability of that individual having both cryptorchidism and hypospadias. As with the year of birth and age of mother models the terms in the model were added individually and the different models compared to assess which terms explain the variation in probabilities between the two groups of cases.

**Figure 20 WinBUGs code for categorical models for Year of Birth and Age of Mother**

```

# Year of Birth group model
model
{
  for (i in 1:n) {DOByr[i] ~ dcat( P[i,1:J] )
    xc1[i]<-Xcoord[i]-mean(Xcoord[i])
    yc1[i]<-YCoord[i]-mean(YCoord[i])
    for (j in 1:J) {
      log(PHI[i,j]) <- beta0 + v[i,j]+beta1*xc1[i]+beta2*yc1[i]+W[area[i]]
    }
    P[i,j] <- PHI[i,j] / sum(PHI[i,1:J])
    v[i,j] ~ dnorm(0, tau.v[j])}

#CAR distribution for the spatial correlated heterogeneity
W[1:regions] ~ car.normal(adj[], weights[], num[], tau.u)
W.mean <- mean(W[])

#Weights
for (i in 1:sumNumNeigh) { weights[i]<-1}

tau.v[1]~dgamma(1,1)
tau.v[2]~dgamma(0.5,0.05)
tau.v[3]~dgamma(0.1,0.0001)
tau.v[4]~dgamma(0.2,0.002)
tau.u ~ dgamma(1, 1)
beta0~dnorm(0,0.1)
beta1~dnorm(0,0.1)
beta2~dnorm(0,0.1)}

# Age of Mother group model
model
{
  for (i in 1:n) {MAgecat[i] ~ dcat( P[i,1:J] )
    xc1[i]<-Xcoord[i]-mean(Xcoord[i])
    yc1[i]<-YCoord[i]-mean(YCoord[i])
    for (j in 1:J) {
      log(PHI[i,j]) <- beta0 + v[i,j]+beta1*xc1[i]+beta2*yc1[i]+W[area[i]]
    }
    P[i,j] <- PHI[i,j] / sum(PHI[i,1:J])
    v[i,j] ~ dnorm(0, tau.v[j])}

#CAR distribution for the spatial correlated heterogeneity
W[1:regions] ~ car.normal(adj[], weights[], num[], tau.u)
W.mean <- mean(W[])

#Weights
for (i in 1:sumNumNeigh) { weights[i]<-1}

tau.v[1]~dgamma(1,1)
tau.v[2]~dgamma(0.5,0.05)
tau.v[3]~dgamma(0.1,0.0001)
tau.v[4]~dgamma(0.2,0.002)
tau.u ~ dgamma(1, 1)
beta0~dnorm(0,0.1)
beta1~dnorm(0,0.1)
beta2~dnorm(0,0.1)}

```

**Figure 21 WinBUGs code for Cryptorchidism/Hypospadias model**

```

model
{
  for(i in 1:n){
    Morph2[i]~dbern(pi[i])
    logit(pi[i])<-beta0 + v[i]+beta[1]*Xcoord[i]+beta[2]*YCoord[i]+W[area[i]]
    v[i]~dnorm(0, tau.v) }

#CAR distribution for the spatial correlated heterogeneity
W[1:regions] ~ car.normal(adj[], weights[], num[], tau.u)
W.mean <- mean(W[])

#Weights
for (i in 1:sumNumNeigh) { weights[i]<-1}
beta0~dnorm(0,2)
for(j in 1:2) {beta[j] ~ dnorm(0.0, 1000)}
tau.v~dgamma(1,1)
tau.u ~ dgamma(1, 1)}

```

### 3.8 Bayesian Hierarchical Multi-indicator model

As it is hypothesised that an environmental factor is associated with the disease/conditions then, if the environmental factor varied across Scotland, it would be expected that the number of cases would also vary geographically. Furthermore, if these disease/conditions are believed to have one underlying environmental cause then it would be expected to find an association between their geographical variations. A multi-indicator model could examine the similarities and differences in the spatial variation in risk between the disease/conditions. It could therefore examine the relationships between the spatial variations of the different disease/conditions.

Another advantage of a multi-indicator model is the potential to reduce the variability of the relative risks estimated. This is particularly applicable with rare conditions, which is the case with these disease/conditions. As seen previously, the random variability of the relative risks estimates is largely due to the sparse counts within postcode sectors. However, a multi-indicator model has the potential for a particular disease to ‘borrow-strength’ from the other indicators. Considering more than one indicator in the model results in an increase in the cases potentially associated with the underlying geographically varying factor, which would reduce the random variability of the estimates within a particular postcode sector. However, in order for this potential reduction in the variability of estimates to occur, the spatial pattern of the relative risks of the indicators included must be similar.

Furthermore, as discussed in Chapter 2, since the start of this research project a multi-indicator approach has been proposed for the analysis of male reproductive health, that compliments the above statistical argument (Skakkebaek, Rajpert-De Meyts, and Main, 2001). The authors recommended that future epidemiological studies on trends in male reproductive health should take into account all aspects of TDS rather than focusing on only one symptom, as important biological information could be lost. As the proposed *in utero* exposure to environmental chemicals occurs at low-doses and the manifestation of some of the symptoms take place several decades since the potential exposure, the strength of the potential association is ‘diluted’. In addition, all the disease/conditions are associated with other risk factors



unrelated to environmental exposure, so potentially further diluting any associations. Therefore Skakkebaek and colleagues are suggesting that taking into account all aspects of TDS would counteract some of this dilution. The combined analysis of various symptoms of TDS, as proposed here with the multi-indicator model, could increase the strength of association between the indicators and the underlying geographically-varying risk factor.

Therefore, while the development of a multi-indicator model is statistically attractive for such data, it is also pertinent to the health problem being investigated.

### 3.8.1 Model

The multi-indicator model is a multivariate extension of the BYM model (3.6.2.4) and the WinBUGs code for this is shown in Figure 22. This model was developed from the two disease model outlined by (Knorr-Held and Best, 2001), so as to include three diseases. A Poisson likelihood is assumed for the observed number of disease  $j$  ( $j=1,..M$ ,  $M=3$ ) in area  $i$  ( $i=1,..N$ ,  $N=895$ ) i.e.

$$y_{ij} \sim \text{Poisson}(e_{ij} \mathcal{G}_{ij}),$$

$$\text{so,} \quad \log \mathcal{G}_{ij} = \alpha_j + u_{ij} + v_{ij}$$

where  $\alpha_j$  represents the disease specific overall relative risk. The heterogeneity terms are multivariate extensions of those specified in the BYM model i.e.  $v_{ij}$  is the uncorrelated heterogeneity with independent multivariate normal priors,

$$v_{ij} \sim \text{mvN}(0, \tau_{vj}^2),$$

therefore the precision of the multivariate priors ( $\tau_{vj}$  in WinBUGs code) have to be specified and are assumed to have a Wishart( $Q, M$ ) distribution.

For the spatial correlated heterogeneity term  $u_{ij}$ , there is multivariate extension of the conditional autoregressive model (CAR) prior used in the BYM model

$$[u_{ij} | u_{1k}, u_{2k}, u_{3k}, i \neq k, \tau_{ij}^2] \sim \text{mvN}(\bar{u}_{ij}, \tau_{ij}^2)$$

where

$$\bar{u}_{ij} = \frac{1}{\sum_k \omega_{ik}} \sum_k u_{jk} \omega_{ik}$$

**Figure 22** WinBUGs code for multi-indicator model

```

model
{
  for(i in 1:N) {
    for(j in 1:M) {
      y[i,j]~dpois(mu[i,j])
      log(mu[i,j])<-log(e[i,j])+a[j]+u[j,i]+v[i,j])
      theta1[i]<-exp(a[1]+u[1,i]+v[i,1])
      theta2[i]<-exp(a[2]+u[2,i]+v[i,2])
      theta3[i]<-exp(a[3]+u[3,i]+v[i,3])
      dev11[i]<-y[i,1]*(log(y[i,1])-log(mu[i,1]))
      dev12[i]<-y[i,1]-mu[i,1]
      dev21[i]<-y[i,2]*(log(y[i,2])-log(mu[i,2]))
      dev22[i]<-y[i,2]-mu[i,2]
      dev31[i]<-y[i,3]*(log(y[i,3])-log(mu[i,3]))
      dev32[i]<-y[i,3]-mu[i,3]
    }
  }
  #MV CAR distribution for the spatial correlated heterogeneity
  u[1:M,1:N] ~ mv.car(adj[], weights[], num[], omega[ , ])
  # Bivariate normal prior for spatial uncorrelated heterogeneity
  for (i in 1:N) { v[i,1:M] ~ dmnorm(zero[],tau[ , ]) }
  #Weights
  for (i in 1:sumNumNeigh)
  { weights[i]<-1}
  eps<-1.0E-6

  # Other priors
  for (j in 1:M) { a[j] ~ dflat() }
  Dhat1<-2*(sum(dev11[])-sum(dev12[]))
  Dhat2<-2*(sum(dev21[])-sum(dev22[]))
  Dhat3<-2*(sum(dev31[])-sum(dev32[]))
  Dhat<-Dhat1+Dhat2+Dhat3
  omega[1:M, 1:M] ~ dwish(R[ , ], M)
  sigma2.u[1:M, 1:M] <- inverse(omega[ , ])
  sigma.u[1] <- sqrt(sigma2.u[1, 1])
  sigma.u[2] <- sqrt(sigma2.u[2, 2])
  sigma.u[3] <- sqrt(sigma2.u[3, 3])
  corr1.u <- sigma2.u[1, 2] / (sigma.u[1] * sigma.u[2])
  corr2.u <- sigma2.u[1, 3] / (sigma.u[1] * sigma.u[3])
  corr3.u <- sigma2.u[2, 3] / (sigma.u[2] * sigma.u[3])
  tau[1:M, 1:M] ~ dwish(Q[ , ], M)
  sigma2.v[1:3, 1:3] <- inverse(tau[ , ])
  sigma.v[1] <- sqrt(sigma2.v[1, 1])
  sigma.v[2] <- sqrt(sigma2.v[2, 2])
  sigma.v[3] <- sqrt(sigma2.v[3, 3])
  corr1.v <- sigma2.v[1, 2] / (sigma.v[1] * sigma.v[2])
  corr2.v <- sigma2.v[1, 3] / (sigma.v[1] * sigma.v[3])
  corr3.v <- sigma2.v[2, 3] / (sigma.v[2] * sigma.v[3])

  #deviance calc for disease 1
  #deviance calc for disease 2
  #deviance calc for disease 3
  #log likelihood
  # Precision matrix of MVCAR
  # Covariance matrix of MVCAR
  # conditional SD of u[1,] (cryp)
  # conditional SD of u[2,] (hypo)
  # conditional SD of u[3,] (tc)
  # within-area conditional correlation
  # between spatial component of
  #variation in the three diseases.
  # Precision matrix of MV Normal
  # Covariance matrix of MV Normal
  # conditional SD of v[1,] (cryp)
  # conditional SD of v[2,] (hypo)
  # conditional SD of v[3,] (tc)
  # within-area correlation between
  # unstructured component of
  # variation in the three diseases

  # within-area conditional correlation between total random effects
  # (i.e. spatial+unstructured components) for between disease correlation
  corr.sum1 <- (sigma2.u[1,2]+sigma2.u[1,2]) /
  (sqrt(sigma2.u[1,1]+sigma2.v[1,1])*sqrt(sigma2.u[2,2]+sigma2.v[2,2]))
  corr.sum2 <- (sigma2.u[1,3]+sigma2.v[1,3]) /
  (sqrt(sigma2.u[1,1]+sigma2.v[1,1])*sqrt(sigma2.u[3,3]+sigma2.v[3,3]))
  corr.sum3 <- (sigma2.u[2,3]+sigma2.v[2,3]) /
  (sqrt(sigma2.u[2,2]+sigma2.v[2,2])*sqrt(sigma2.u[3,3]+sigma2.v[3,3]))
}

```



$$\text{and} \quad \tau_{ij}^2 = \frac{\tau_{ij}^2}{\sum_k \omega_{ik}}, \quad \omega_{ik} = 1, \text{ if } i, k \text{ are neighbours (0 if they are not).}$$

So the distribution of the log relative risk in postcode sector  $i$  for disease  $j$  is normal with mean given by the mean of the log of the relative risks in the neighbouring postcode sectors for that disease and the variance being proportional to the number of neighbouring postcode sectors.

In WinBUGs the multivariate CAR is specified as `mv.car` for the  $M \times N$  matrix of random variables  $\mathbf{U}$ , where columns of  $\mathbf{U}$  represent the postcode sectors and rows represent the diseases (i.e. opposite from the other specified terms). The syntax for this distribution is as follows:

$$u[1:M, 1:N] \sim \text{mv.car}(\text{adj}[], \text{weights}[], \text{num}[], \text{omega}[, ])$$

where `adj[]`, `weights[]`, `num[]` are the same outlined for the BYM model. The only difference is the precision matrix of the multivariate intrinsic Gaussian CAR prior `omega[, ]`. As with the uncorrelated heterogeneity, the precision of the multivariate priors for the spatially correlated heterogeneity are assumed to have a  $\text{Wishart}(R, J)$  distribution.

Table 13 describes the other parameters specified in the multivariate model detailed in Figure 22. The comparison of indicators' relative risks is done by comparing one with another so as to investigate which of the three indicators have a between postcode sector correlation and whether it is spatially or randomly structured. The correlation of the spatially structured heterogeneity between two particular diseases is estimated by `corr#.u`, while the correlation of the spatially unstructured heterogeneity between two diseases is estimated by `corr#.v`. The correlation of the total heterogeneity between two diseases is estimated by `corr#.sum`. These three terms are compared to see if the two diseases have a between area correlation and whether this is due to geographically-varying unexplained risk or a non geographically-varying unexplained risk.

The intercept terms for the three diseases (`a[#]`) represent the logarithm of the overall disease-specific relative risk.



**Table 13 Descriptions of parameters included in Multi-Indicator model**

Parameter	Description of parameter
a[1]	Intercept term for Cryptorchidism model
a[2]	Intercept term for Hypospadias model
a[3]	Intercept term for Testicular Cancer model
corr.sum1	Within-area correlation between total heterogeneity of Cryptorchidism and Hypospadias
corr1.u	Within-area correlation between spatial heterogeneity of Cryptorchidism and Hypospadias
corr1.v	Within-area correlation between random heterogeneity of Cryptorchidism and Hypospadias
corr.sum2	Within-area correlation between total heterogeneity of Cryptorchidism and Testicular Cancer
corr2.u	Within-area correlation between spatial heterogeneity of Cryptorchidism and Testicular Cancer
corr2.v	Within-area correlation between random heterogeneity of Cryptorchidism and Testicular Cancer
corr.sum3	Within-area correlation between total heterogeneity of Hypospadias and Testicular Cancer
corr3.u	Within-area correlation between spatial heterogeneity of Hypospadias and Testicular Cancer
corr3.v	Within-area correlation between random heterogeneity of Hypospadias and Testicular Cancer
sigma.u[1]	Standard Deviation of spatial heterogeneity of Cryptorchidism
sigma.u[2]	Standard Deviation of spatial heterogeneity of Hypospadias
sigma.u[3]	Standard Deviation of spatial heterogeneity of Testicular Cancer
sigma.v[1]	Standard Deviation of random heterogeneity for Cryptorchidism
sigma.v[2]	Standard Deviation of random heterogeneity for Hypospadias
sigma.v[3]	Standard Deviation of random heterogeneity for Testicular Cancer

For each of the diseases, the variability of the heterogeneity estimates is summarised by the standard deviation. In the WinBUGs code, the standard deviations are estimated by sigma.u(#) (spatially correlated heterogeneities) and sigma.v(#) (spatially uncorrelated heterogeneities).

As will be detailed later (3.9.3) an overall goodness of fit measure (D.I.C) is calculated in WinBUGs for all the models in this project. However, this tool is currently not available when the mv.car distribution is used. Therefore, this measure had to be calculated in the model. The D.I.C is calculated as,

$$DIC = \bar{D} - pD = 2 * \bar{D} - \hat{D}$$

where  $\bar{D}$  is the deviance which is pre-defined in WinBUGS and so can be estimated from the posterior distribution like other parameters.  $\hat{D}$  is the conditional log likelihood, and needs to be specified in the model. In the case of a Poisson model it is

$$\hat{D} = 2 \left[ \sum_{i=1}^n y_i (Ln(y_i) - Ln(mu_i)) - \sum_{i=1}^n (y_i - mu_i) \right]$$

which needs to be calculated for each indicator and then summed to provide the overall model's conditional log likelihood.

### 3.9 Bayesian Modelling Software – WinBUGs

As already mentioned the analysis of these data has been done using the package WinBUGs. WinBUGs was developed by the Medical Research Council Biostatistics Unit at Cambridge University. The program is currently free to download at <http://www.mrc-bsu.cam.ac.uk/bugs/> and comes with a wide range of documentation and examples. This section describes the basics of the package – what data are required to run models; the checks required and how the results produced by the models were assessed.

#### 3.9.1 Running a model in WinBUGs

There are three pieces of information required by WinBUGs to run a Bayesian model:

- (i) **The model** file specifies the likelihood and priori distributions and the accompanying data. It can be developed graphically via DoodleBUGs which allows the user to describe the models in terms of graphs. However, as many features of BUGs language cannot be expressed using the graphical interface, all models within the research project were specified via the text-based BUGs language and have been shown for each stage of analysis.
- (ii) **The data** is specified in the model file but is introduced as a separate file and there are particular formats in which WinBUGs reads data.
- (iii) **Initial values** are required for those priors for whom no data are known nor provided e.g. hyper-parameters. They can either be entered in the same format as the data file or WinBUGs will generate initial values from the specified prior or an approximation to it. If initial values are given this can sometimes help convergence occur sooner.

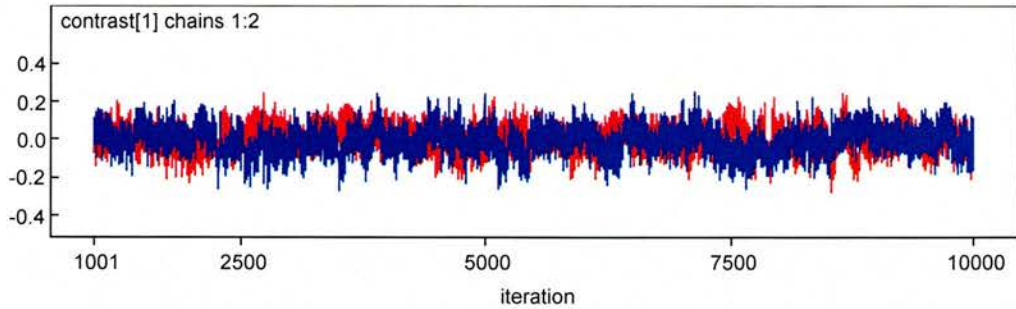
#### 3.9.2 Checking convergence

In order to produce posterior estimates, samples are taken from the posterior distribution. Before samples can be taken it is necessary to assess if the iterative simulations have reached an equilibrium distribution – known as convergence. To check for convergence in WinBUGs, it is recommended to use a combination of diagnostics and visual inspection of trace plots (Lawson, Browne, and Vidal Rodeiro, 2003).



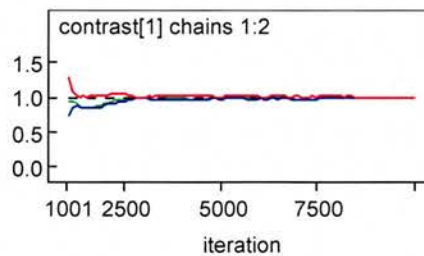
The visual inspection of trace plots consists of running parallel chains and looking at the histories of the parameters produced by the model. The history plots the value of the parameters against the number of iterations. If the parameter is converged then the history plot should look like the figure below.

**Figure 23** Example of a history plot for which a parameter has converged



The convergence diagnostic produced in WinBUGs is the Gelman-Rubin diagnostic (Brooks and Gelman, 1998). It is based on running parallel chains from different initial values. The Gelman-Rubin plot shows three values over the iterations: a green line represents the width of the central 80% interval of the pooled runs; a blue line represents the average width of the 80% intervals within the runs; and the red line represents the ratio of the pooled/within runs. Convergence is believed to be reached when the ratio converges to 1, while the pooled and within values have reached stability (Brooks and Gelman, 1998). Figure 24 shows the Gelman-Rubin plot produced by WinBUGs for a converged parameter, the red line has converged on 1 and the blue and green line have stabilised.

**Figure 24** Example of a Gelman-Rubin plot for which a parameter has converged



Therefore before any posterior samples were taken from any of the models described previously, convergence was tested by visual assessment of the history plot and the Gelman-Rubin plot on running two parallel chains. On convergence, further iterations were run from which samples were taken to obtain posterior inferences.



The number of further iterations required for accurate posterior estimates was assessed by using the Monte Carlo standard errors (MC error) of the parameters which is produced by WinBUGs when posterior samples are requested. It is recommend that the MC error, i.e. the standard deviation of the difference between the mean of the sampled values and the true posterior mean, should be small compared to the posterior standard deviation (Lawson, Browne, and Vidal Rodeiro, 2003). For all the models reported, the estimates were assessed to be accurate when the MC error was at least 5% of the posterior standard deviation.

### 3.9.3 Assessment of models

As three Bayesian Hierarchical disease count models were run to attempt to explain the spatial variation of the relative risks these models performance need to be compared and assessed. Indeed with any modelling, an assessment of the models via an analysis of the residuals should be carried out. The standardised residuals  $r_i$  were used and are calculated for each postcode sector  $i$  as:

$$r_i = \frac{\{y_i - \hat{y}_i\}}{\sqrt{\text{var}(y_i - \hat{y}_i)}}$$

where  $y_i$  is the observed count,  $\hat{y}_i$  is the fitted values due to the model i.e. expected count  $\times$  estimated relative risk and  $\sqrt{\text{var}(y_i - \hat{y}_i)}$  is the standard deviation of the standardised residuals.

There are assumptions placed on the standardised residuals which require testing and these have been shown for each of the disease count models. The normal plot of the standardised residuals should follow the  $x=y$  line; and when the standardised residuals are plotted against the fitted values, the standardised residuals should be evenly scattered at all the fitted values.

Also shown for each of the disease count models are the maps of the standardised residuals by postcode sectors. These maps are used to visually assess if there is any spatial correlation of the standardised residuals i.e. are there clusters. Furthermore, the spatial correlation of the standardised residuals can be tested formally using the Moran's I, which is also included for the residuals of each disease count model.

As previously mentioned several models have been compared in the analysis, either to see which models fits the data better or to see if the inclusion of possible covariates within a particular model might explain any spatial variation. The Deviance Information Criterion (DIC) diagnostic is the overall goodness of fit measure developed for WinBUGs (Spiegelhalter *et al.*, 2002), and is used for all the comparison of models. The values produced by the diagnostic are the deviance and the DIC which is the deviance value that takes into account the number of parameters within the model. For a model to be a significantly better fit to data than another model, it is recommended that there is a difference of 2 between the DIC values.

### **3.10 Summary of Research Project**

This chapter has outlined the research project and this final section aims to summarise this.

Firstly the aims of the research project were outlined and discussed in relation to current research. These aims of the study attempt to:

- give a complete picture of the spatial variation of three indicators of male reproductive health in Scotland.
- explain any geographical variation found in these disease/conditions; and so investigate the possible underlying environmental exposure hypothesised to be associated with male reproductive health.
- overcome the two unresolved issues highlighted in previous research, namely the quality of the diseases/conditions data and the conjoint analysis of these indicators.

Before describing the research project in more detail it was necessary to introduce some key concepts of spatial epidemiology, as these would determine the data used and its subsequent analysis.

- To achieve the aims of the research project the following types of analyses would be carried out on disease count data: disease mapping, non-focused clustering and ecological analysis.
- There are cartographic and visual cognition issues that have consequences on the maps presented in this research project, namely;



- (i) thematic maps are produced;
  - (ii) for maps of the same disease/condition the same cut-off values are used;
  - (iii) a close-up of the Central Belt is produced for most maps;
  - (iv) blue is chosen as the colour gradient with darker shades for higher values and lighter for lower;
  - (v) the boundaries of the postcode sectors are not illustrated.
- The use of disease count data may introduce ecological bias where inferences made about the spatial variation of the risk between postcode sectors does not necessarily translate to the individuals within those postcode sectors.

The datasets used in the study were described and classified into four categories depending on its use within the research project;

- the three specific diseases for which the geographical distributions are to be described are cryptorchidism, hypospadias and testicular cancer. In Scotland these Male Reproductive Health Disease/Condition datasets are of a high quality i.e. consistently collected across geography and time, therefore potentially overcoming unresolved issues highlighted in previous research;
- birth and population data are used to standardise particular male reproductive health diseases/conditions by the underlying population at risk;
- the 1991 Census postcode sector boundary data are used in all maps to show the geographical distribution of the male reproductive health disease/condition in Scotland;
- a rural/urban indicator, 2 deprivation indices and 2 radon measurements are used to explore if they explain the geographical distributions of the male reproductive health disease/condition data.
- all data are geo-referenced on postcode sector and as these change over time they need to be assigned to one common geography; the methods used to assign all postcode sector to those postcode sector boundaries valid as at 1991 census are described and discussed.

There are four analyses carried out on the disease count data separately to estimate the relative risk per postcode sector in Scotland. The first is the calculation of the Standardised Morbidity Ratios (SMRs). Although the SMRs take into account the



size of the population at risk within each postcode sector, they can be dominated by the uncertainty of the estimates, particularly in areas with small number of cases. In order to account for the variability of the relative risk estimates, that might either be randomly or spatially structured, Bayesian Hierarchical modelling was used.

Three Bayesian Hierarchical Models were used to estimate the relative risks per postcode sectors in Scotland. Each model makes different assumptions about the spatial variation of the relative risks and the following table summaries these three models in terms of these assumptions.

**Table 14 Summary of the 3 Bayesian Hierarchical disease count models**

Model	Likelihood on cases	Prior on SMRs (crude relative risks (RRs))	Posterior estimates of RRs smoothed towards	Include covariates?
Poisson-Gamma	Poisson	Gamma	Global Mean RR	No
Log-Normal	Poisson	Normal on log of SMRs	Global Mean RR	Yes
BYM	Poisson	Normal on log of SMRs	Global Mean RR and RRs of neighbours	Yes

Furthermore:

- The potential covariates (a rural/urban indicator, 2 deprivation indices and 2 radon measurements) were included to the Log-Normal and BYM models to see which factors explain the spatial variation of the different disease/conditions.
- To compare the success of all the Bayesian Hierarchical models, an analysis of the residuals would be conducted and a comparison of the DIC diagnostics.
- The BYM model was extended so as to analyse the three disease/conditions conjointly. This conjoint model potentially would reduce the variability of the estimates but also explore the spatial relationships between the three disease/conditions relative risks.

To assess the possibility of ecological fallacy in these disease count models, individual level Bayesian models were developed.

- The spatial analysis was conducted on particular individual level information concerning the cryptorchidism cases (Year of Birth, Age of Mother and co-morbidity), to give an example of the potential of such analysis due to time constraints.

- A number of Bayesian models for each particular individual level information are required to ascertain the extent to which effects (spatial and non-spatial) explain any differences between the groups of individuals in each of these individual level covariates.
- If the geographical variation of these groups of individuals were similar to that of the geographical variation of the cryptorchidism risk, then it is possible that this individual information explains the geographical variation in the relative risk rather than area-specific risk factors.

## **Chapter 4 : Cryptorchidism Analysis**

### **4.1 Introduction**

This chapter details the analysis of the cryptorchidism dataset described in Chapter 3, where the methods used are also outlined. Specific methods sections of that chapter are referred to at the relevant points within the results.

The results of the analysis are detailed in seven sections, the first summarises the cryptorchidism dataset. The next five sections contain the area-specific spatial analysis of cryptorchidism in Scotland. The first is a summary of the initial spatial analysis – the SMRs, while the next three summarise the results of applying the three Bayesian spatial models to the cryptorchidism dataset. The final area-specific spatial analysis section outlines the results of including potential covariates within the Bayesian models to explain the spatial variation of the relative risks. The final results section shows the results of the individual level analysis carried out on the cryptorchidism data to investigate the possibility of ecological bias.

The chapter is completed with a summary of the conclusions of the cryptorchidism analysis and highlights points for further discussion.

### **4.2 Summary of cryptorchidism dataset**

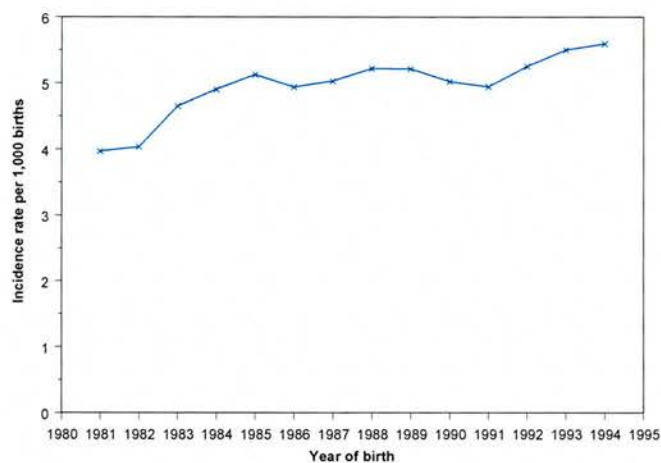
Further information pertaining to each of the cryptorchidism cases was requested as part of the dataset (Appendix 1). This was done as the geographical variation of cryptorchidism may be explained by this information rather than area-specific factors. This section summarises those factors that will be included in the individual level models (4.8).

#### **4.2.1 Incidence over time**

The incidence of births with cryptorchidism appears to increase with time in Scotland (Figure 25), a pattern which has been found in previous research (Ansell et al., 1992). The changes over time in incidence might also vary geographically. Therefore a spatial model would assess if the year of birth of the cryptorchidism cases varies geographically, and so might explain any geographical variation in cryptorchidism.



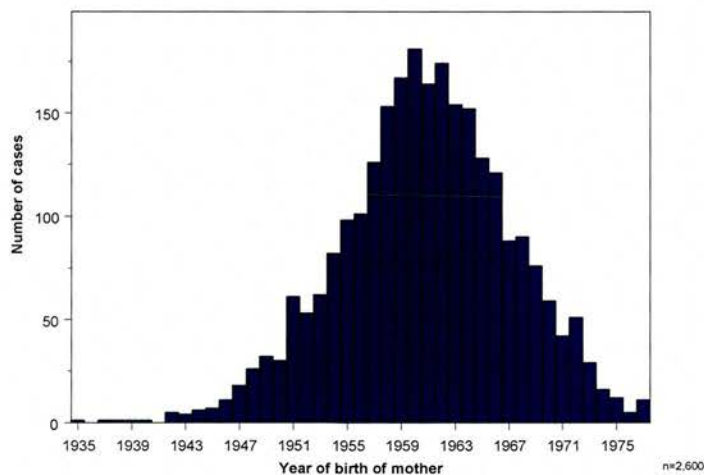
**Figure 25** Cryptorchidism incidence rate per 1,000 births (3 year moving average)



**4.2.2 Mothers’ year of birth**

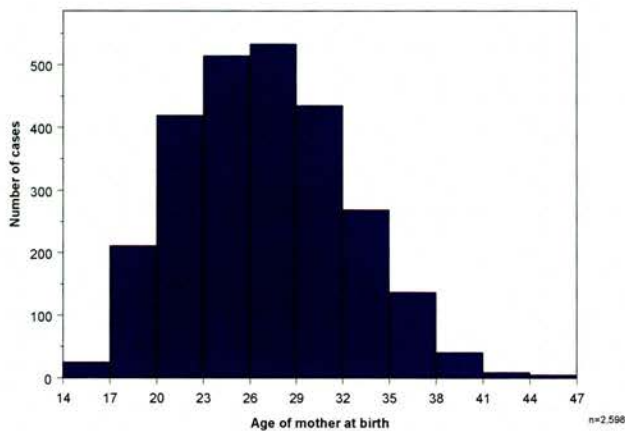
For those cryptorchidism cases that had accompanying details on their mother (n=2,600) we would be able to see if information about these mother’s might have an association with any spatial variation. Firstly, the year of birth of the mother ranged from 1935 to 1978, with a mean of 1960 and its distribution is approximately normally distributed (Figure 26).

**Figure 26** Histogram of Mothers’ Year of Birth



As the month and year of birth of the mother’s are known it would be possible to calculate the mother age when their son was born. Figure 27 shows the distribution of the mothers’ ages, which range from 14 to 45 with a mean of 26.5 years.

Figure 27 Histogram of mother’s age at son’s birth



4.3 Standardised Morbidity Ratio (SMR) maps

The methods used to calculate the SMRs for each 1991 postcode sector are outlined in 3.6.1. The following gives the results of these calculations in relation to the cryptorchidism dataset.

4.3.1 Observed number of cryptorchidism cases per 1991 postcode sector

Of the 2,635 cases of cryptorchidism, 12 records did not have postcode sector recorded. Therefore 2,623 cases were linked to the database created that matches all valid postcode sectors to where this would have been in 1991 (detailed in 3.5). Of the 691 postcode sectors recorded in the cryptorchidism dataset, only 679 were linked to records within the 1991 database. The remaining 12 postcode sectors were not valid postcode sectors; and are detailed in Table 15.

Table 15 Description of invalid postcodes in cryptorchidism dataset

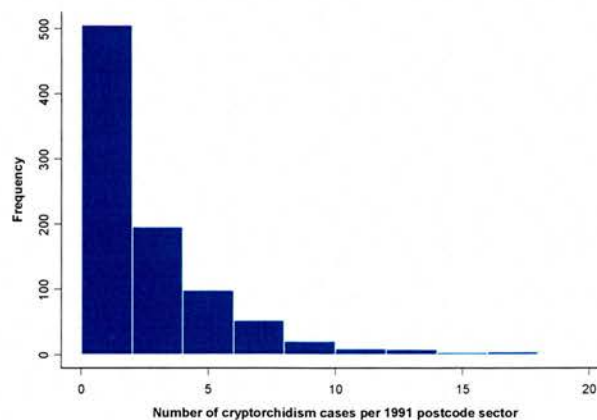
Description of invalid postcode sector	Number of postcode sectors (number of cases of cryptorchidism)
Mistyped postcode sector	4 postcode sectors (4 cases)
English postcode sector	1 postcode sectors (4 cases)
Local Council code	7 postcode sectors (92 cases)

Of those postcode sectors mistyped, 1 (1 case) could be corrected. However none of the remaining postcode sectors could be geographically referenced resulting in 99 cases being excluded from further analysis. This exclusion was valid for those cases with English postcode sectors, which probably resulted from cross-boundary

attendance at a maternity hospital. However, the high number of cases lost in some areas due to local council codes being used instead of postcode sectors does impact on subsequent spatial analysis. Local council codes are used instead of postcode sectors when an address is not known and are at much lower spatial resolution. Therefore, those cases with local council codes can not be assigned to postcode sectors as local councils cover several postcode sectors. When further investigation was carried out on which local council codes were used it would appear that a particular area of Scotland predominately used these codes. While most local councils were only used once or twice in the dataset, 3 are used considerable more; Kirkcaldy (40 cases), North East Fife (14 cases) and Dunfermline (34 cases). These are in the same locality and furthermore, it would appear that these cases all originated from two hospitals in the locality. It is not clear why this has occurred in both the cryptorchidism and hypospadias datasets, but the result is that these areas of Scotland will have under-reported cases of both diseases; which should be remembered in subsequent assessment of the maps.

Therefore, of the 2,635 cases of cryptorchidism 2,524 could be assigned to a 1991 postcode sector. The distribution of the number of cryptorchidism cases per 1991 postcode sector is shown in Figure 28. As can be seen, the distribution is highly skewed - the number of cases in each postcode sector ranges from 0 to 19 with a median of 2 cases.

**Figure 28** Histogram of the number of cryptorchidism cases per 1991 postcode sectors



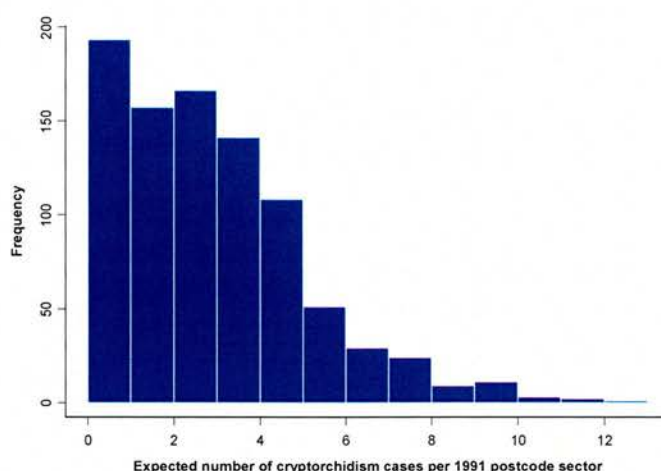


### 4.3.2 Expected number of cryptorchidism cases per 1991 postcode sector

The expected numbers of cryptorchidism cases per 1991 postcode sector have been calculated using the methods described in detail in 3.6.1. The cryptorchidism expected numbers were standardised by year of birth and the underlying population used was all births within the linked maternity database.

The distribution of the expected cryptorchidism cases in the 1991 postcode sectors is shown in Figure 29. While the distribution is skewed, it is not as extreme as the observed values - The range of expected cases within the postcode sectors is 0 to 12.04, with a median of 2.52 cases.

**Figure 29** Histogram of the expected number of cryptorchidism cases per 1991 postcode sectors

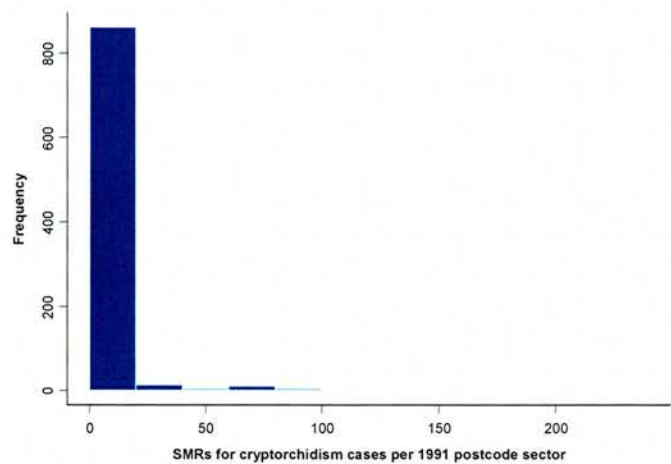


### 4.3.3 SMRs of cryptorchidism cases per postcode sector

With the observed and expected values for each 1991 postcode sector calculated, the SMR for each could be calculated. The distribution of the SMRs is highly skewed (Figure 30).

There are three values that are very extreme – 235.61, 179.65 and 106.35. Comparison of these values with the third quartile of 1.77 shows how skewed the distribution is. These extreme values are a result of small expected values. The mean SMR is 3.78 (standard deviation 14.8) while the median is 0.78.

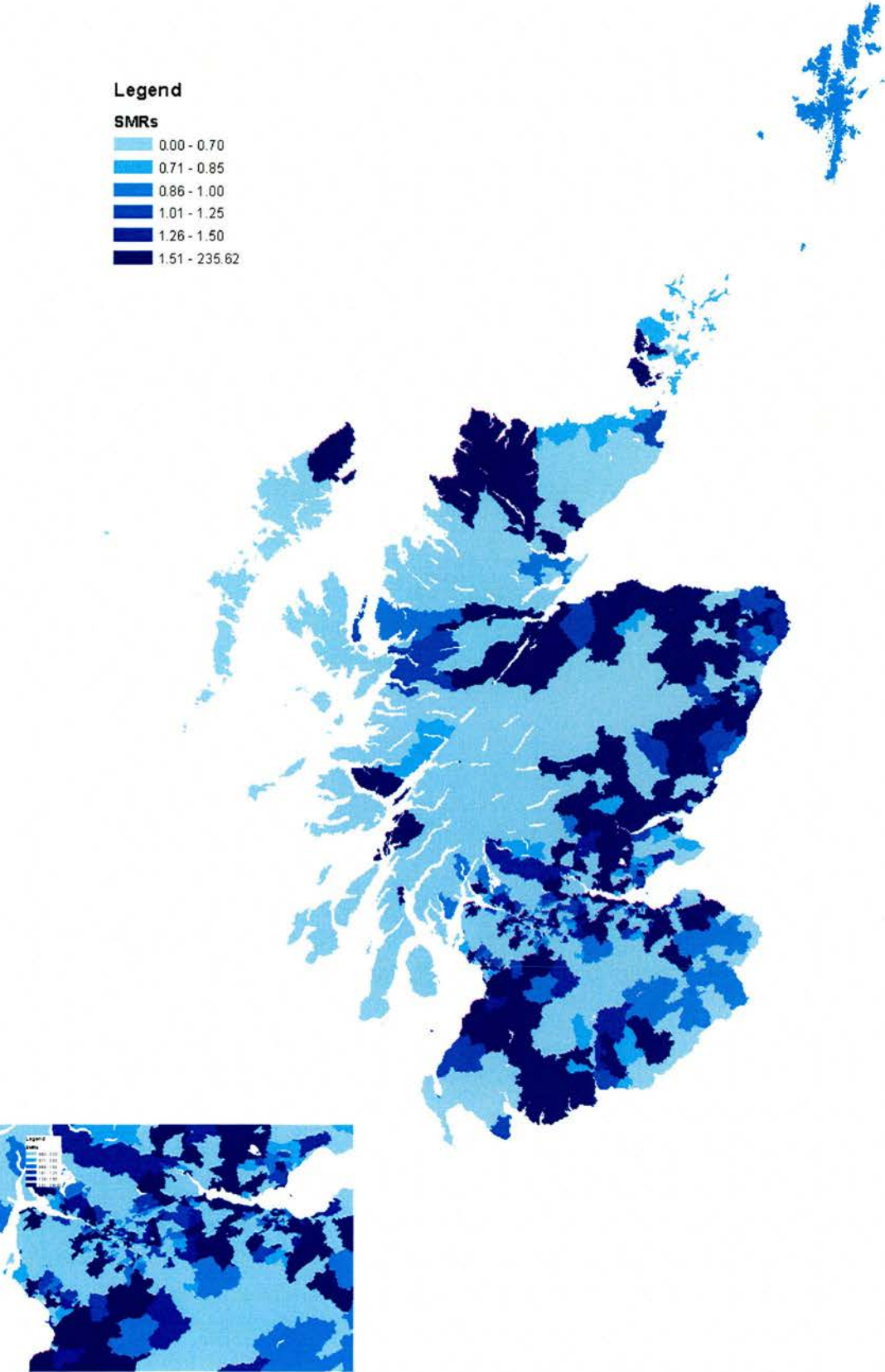
**Figure 30** Histogram of cryptorchidism SMRs per 1991 postcode sector



There are geographical variations in the SMRs across Scotland (Figure 31) shows the maps of these values. There appears to be clustering of higher SMRs in the North-East and South-West of Scotland and clustering of the lower SMRs in the North-West and South East.

As discussed in 3.6.1, SMRs are prone to high variability especially when used with areas with small number of cases. Cryptorchidism is the lowest incidence of the three conditions studied in the research project so SMR variability will be particularly pertinent here. The variability of the estimates of the SMRs is assessed by calculating the standard error of each SMR, the methods for which are also detailed in 3.6.1. The distribution of the standard errors is, as the SMR distribution, very skewed. The maximum value is 235.62 with a medium of 0.92. The maximum SMR (235.62) has the same standard error value, as the observed count within this postcode sector is 1.

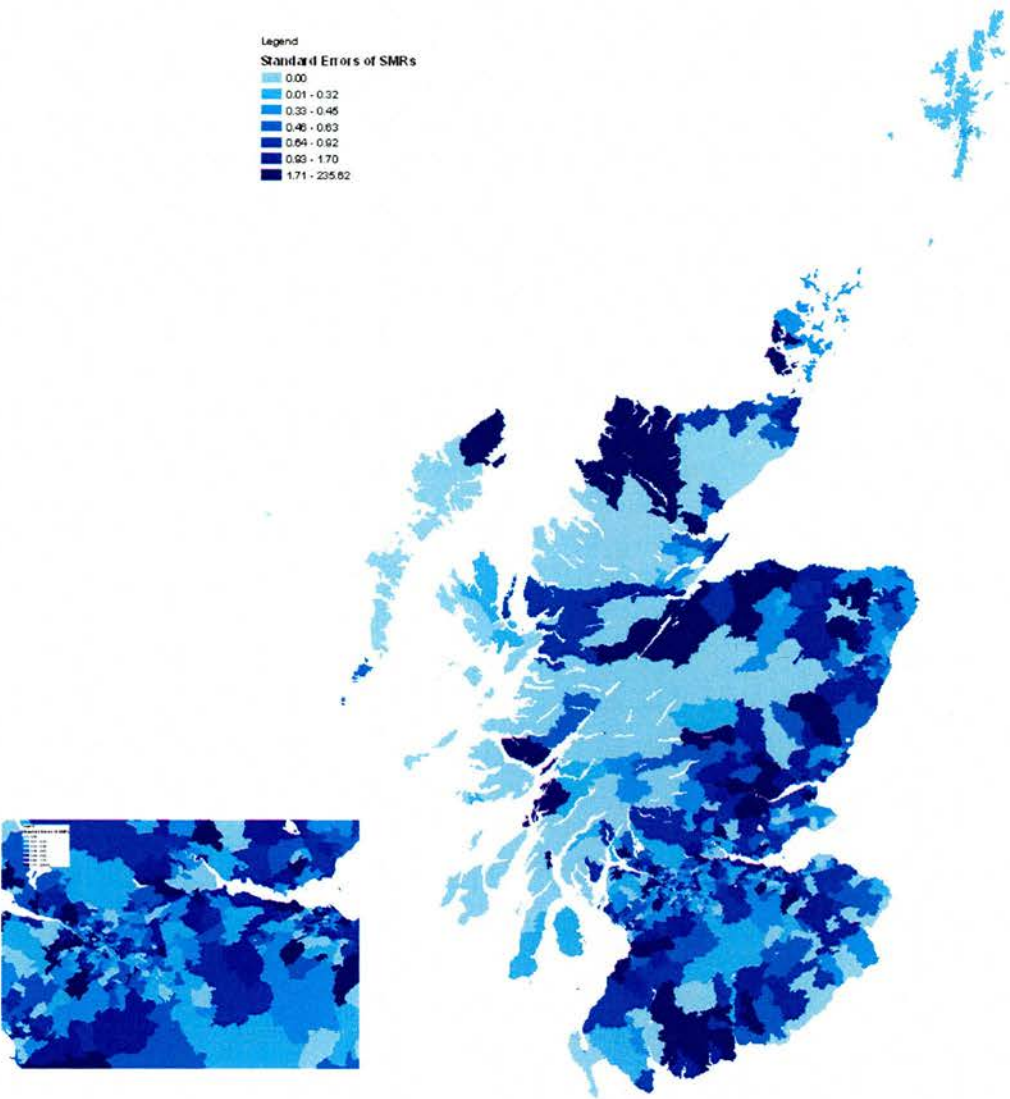
**Figure 31** SMRs per 1991 postcode sectors for Cryptorchidism: Scotland and Central Belt 1980-1999





The maps of the standard errors of the SMRs are shown below.

**Figure 32** Standard error of SMRs per 1991 postcode sector for Cryptorchidism: Scotland and Central Belt 1980-1999



It would appear that the clustering of the standard errors is similar to that of the SMRs. Therefore the SMRs appear to reflect the random variation of the estimates rather than any variation in disease risk. This variability in the standardised rates reflects both the small number of cases and the variation in population density across the postcode sectors. Therefore this initial analysis is limited in being able to show the spatial variation of the cryptorchidism SMRs over Scotland. Therefore it looks important to take into account this variability when calculating the cryptorchidism disease risk, which can be done with Bayesian models.

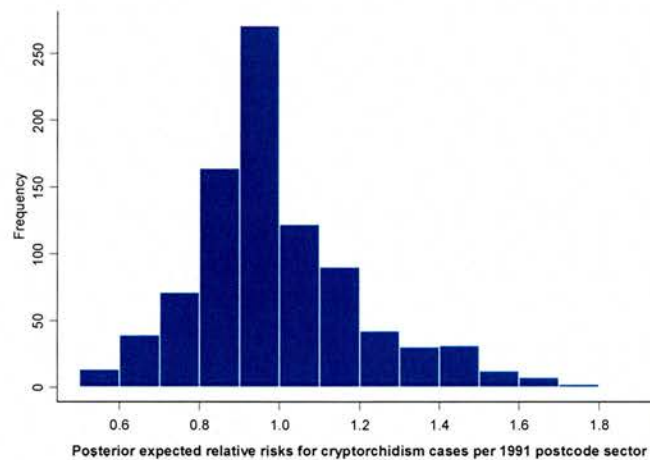
## 4.4 Bayesian Hierarchical Models of cryptorchidism count data – Poisson-Gamma

As discussed in more detail in 3.6.2.2, the Poisson-Gamma model smooths the relative risks towards the overall mean relative risk and so decreases the range of their values and variability. The model was run with the cryptorchidism dataset using WinBUGs and converged following 4,000 iterations. To produce robust posterior estimates a further 20,000 iterations were run.

### 4.4.1 Posterior estimates from model

The distribution of the posterior expected relative risks for each of the 1991 postcode sectors as produced by the Poisson-Gamma model is shown in Figure 33.

**Figure 33** Histogram of Cryptorchidism posterior expected Relative Risk estimated from the Poisson-Gamma model



The distribution is less skewed than that for the SMRs (median 0.97 and mean 0.99) and as expected the range of values has been reduced (0.53, 1.8) towards the overall mean. As the population mean relative risk is 0.99 with a standard deviation 0.026, the variability of this estimate has also been reduced compared to the SMR (Table 16).

**Table 16     Posterior estimates for parameters in Poisson-Gamma model**

Parameter	Mean	Standard Deviation	MC error	2.5% credible interval	Median	97.5% credible interval
a	5.94	0.774	0.05189	4.593	5.88	7.703
b	5.98	0.7943	0.05329	4.615	5.912	7.79
mean	0.9947	2.57E-02	4.71E-04	0.9455	0.9942	1.046
var	0.1693	0.0232	0.001475	0.1266	0.1683	0.2186

With the change in the variability of the estimates of the relative risks, the spatial variation of the relative risks has been smoothed compared to the SMRs (Figure 34). Even with the reduction in the variability of the estimates, the clustering of the higher relative risks remains in the North-East of Scotland.

The probabilities of the relative risks being greater than 1 show a similar spatial pattern to the relative risks map, so confirming those areas with high and low relative risks while taking into account the variability of these estimates (Figure 35).



**Figure 34** Posterior mean relative risks per 1991 postcode sector for Cryptorchidism from the Poisson-Gamma model: Scotland 1980-1999



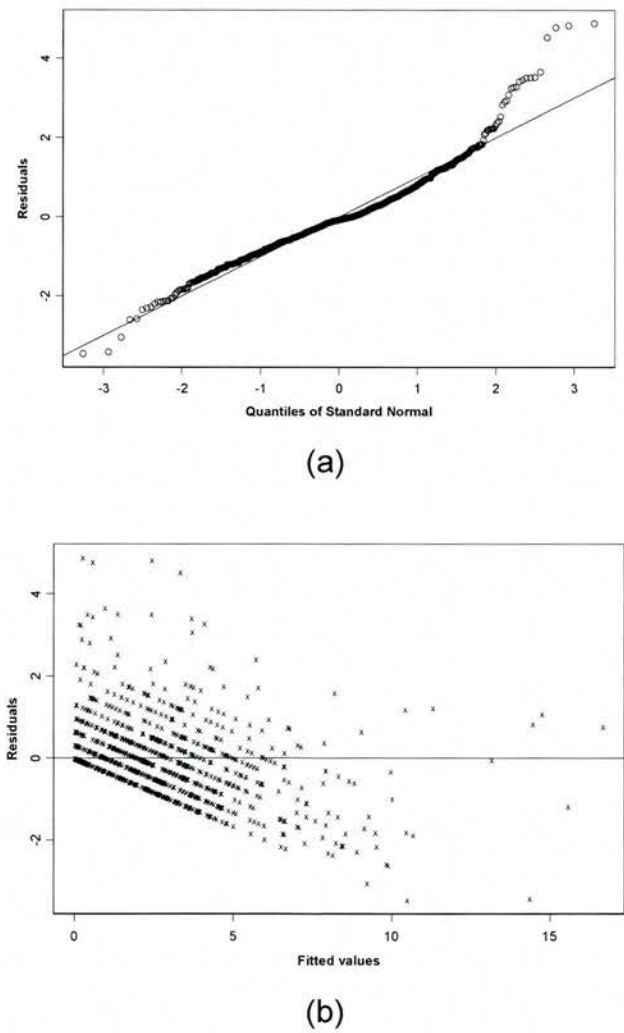
**Figure 35** Posterior probabilities of relative risks per 1991 postcode sector for Cryptorchidism from the Poisson-Gamma model: Scotland 1980-1999



4.4.2 Assessment of model

The relative risk estimates have been smoothed by the Poisson-Gamma model, but is the model successful at fitting the cryptorchidism data? In order to assess the model an analysis of the standardised residuals is undertaken, as outlined in 3.9.3, and is shown in Figure 36. The Normal Plot of the residuals (a) should follow the  $x=y$  line, which is not the case for the extreme cases in particular the high relative risks. For the residuals plotted by the fitted values (b), the residuals should be evenly scattered at all the fitted values, this is not the case. Therefore the Poisson-Gamma model is not a successful fit of the higher relative risk values of the cryptorchidism data.

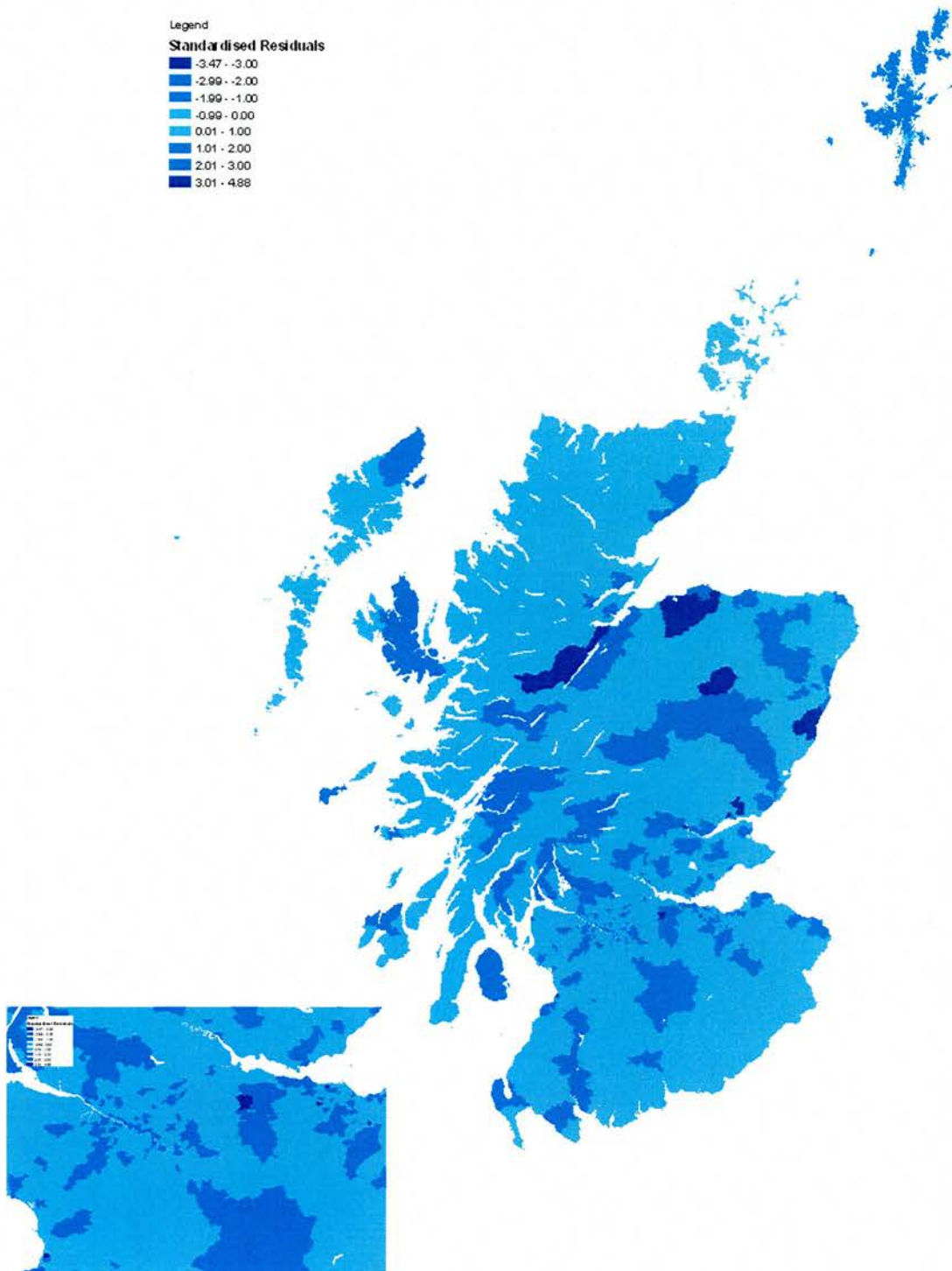
Figure 36 Poisson-Gamma Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted





Furthermore, there appears to be some spatial correlation of the residuals in particular in the North-East of Scotland (Figure 37).

**Figure 37** Standardised Residuals of Poisson-Gamma model for Cryptorchidism: Scotland and Central Belt 1980-1999



The spatial correlation of the residuals can be tested formally using the Moran’s I test (Table 17).

**Table 17    Moran’s I test result for residuals from Poisson-Gamma model**

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.19 (0.15, 0.23)
Correlation Normal p-value (2-sided)	$4.4 \times 10^{-4}$
Mean Permutation correlations (Inter-quartile range)	-0.002 (-0.016, 0.0113)
Permutation p-value	<0.00001

There does appear to be a statistically significant ( $p=4.4 \times 10^{-4}$ ) spatial correlation of the residuals, although it is not a very strong one ( $r=0.19$ ). Furthermore, as the permutations do not appear to be correlated ( $r=-0.002$ ), then the test is valid. Therefore as the residuals appear to cluster in areas where high relative risks are estimated, then the models does not fully explain the variability of these estimates.

**4.4.3 Conclusions for Poisson-Gamma Model**

While the Poisson-Gamma model smoothes the relative risks and so decreases the range of their values, it does not fully take into account the variability of the cryptorchidism estimates. In particular, the model is least successful for those areas with high relative risks. As there appears to be some clustering of the residuals, it might be that a term that accounts for spatially correlated heterogeneity should be included within a model for the cryptorchidism data.

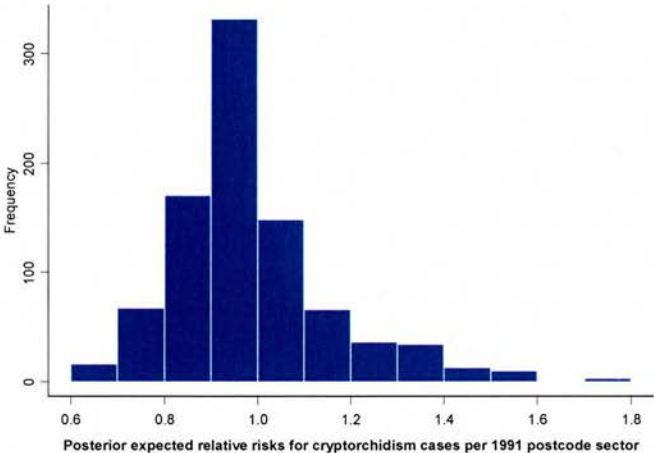
**4.5 Bayesian Hierarchical Models of cryptorchidism count data – Log-Normal**

The Log-Normal model smoothes the relative risk estimates towards the overall mean relative risk as with the Poisson-Gamma, but unlike the Poisson-Gamma it is possible to include additional terms. As detailed further in 3.6.2.3, a spatially uncorrelated heterogeneity term is the only term added to this model. This term assumes that any variability in the relative risk estimates is random and not spatially structured; a spatially structured heterogeneity term will be added in the BYM model which is detailed in 4.6. The Log-Normal model converged following 2,000 iterations with a further 10,000 were run to produce robust posterior estimates.

4.5.1 Posterior estimates from model

The distribution of the cryptorchidism posterior expected relative risks for each of the 1991 postcode sectors as produced by the Log-Normal model is shown in Figure 38. It has a similar distribution of relative risks as the Poisson-Gamma model (median 0.97 and mean 0.99), although has a narrower range of values (0.65-1.75) compared to the Poisson-Gamma (0.53, 1.8).

Figure 38 Histogram of Cryptorchidism posterior expected Relative Risk estimated from the Log-normal model



Therefore, the Log-Normal model reduces the range of values compared to the SMRs and those produced by the Poisson-Gamma model. As already mentioned the Log-Normal smoothes the relative risk estimates towards the overall mean relative risk, which for the cryptorchidism data is 0.93 with a standard deviation of 0.02 (Table 18).

Table 18 Posterior estimates for parameters in Log-Normal model

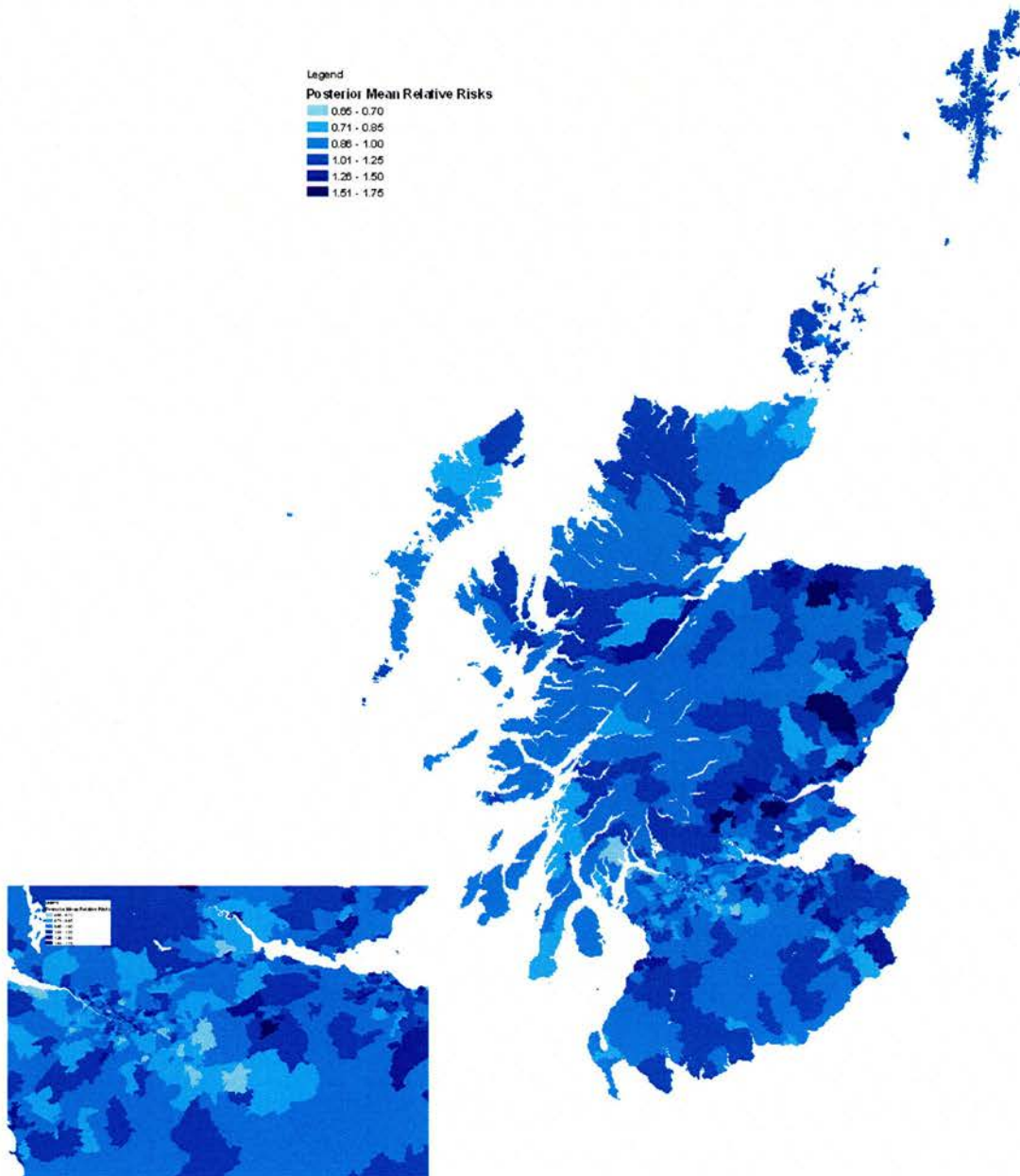
Parameter	Mean	Standard Deviation	MC error	2.5% credible interval	Median	97.5% credible interval
alpha	-0.07081	0.02635	5.22E-04	-0.1238	-0.07066	-0.02095
mean	0.932	0.02454	4.85E-04	0.8836	0.9318	0.9793
tau.v	8.59	1.744	0.07418	5.96	8.315	12.64

So the population mean relative risk produced by the Log-Normal is lower than that produced by the Poisson-Gamma model but higher than the median SMRs. The variability of this estimate has been reduced compared to the SMR and to the same extent as that done by the Poisson-Gamma model. The spatial variation of the



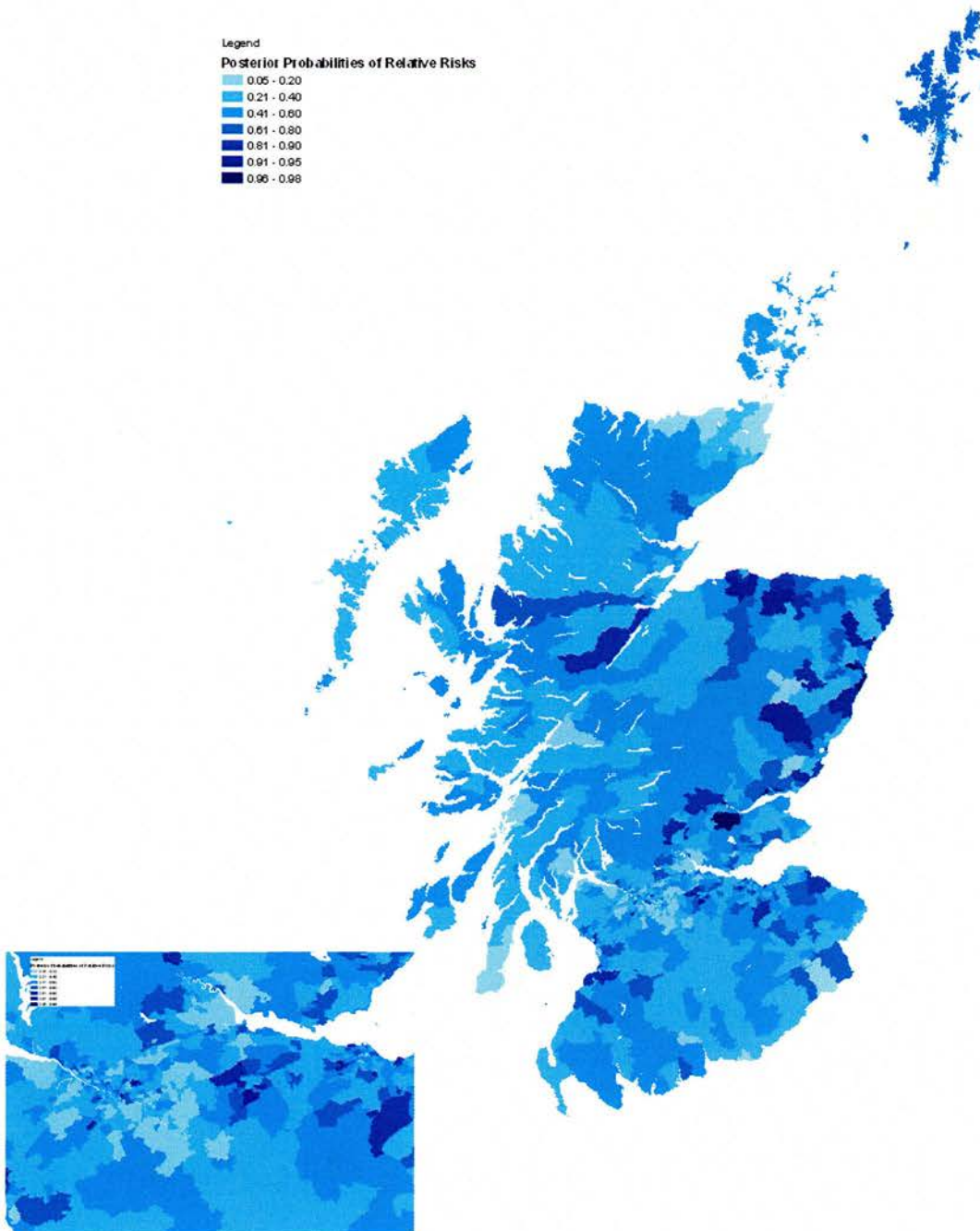
relative risk estimates produced by the Log-Normal model is very similar to that produced by the Poisson-Gamma model (Figure 39). Again we can see the North-East has a cluster of elevated cryptorchidism risk, although they are only slightly elevated.

**Figure 39** Posterior mean relative risks per 1991 postcode sector for Cryptorchidism from the Log-normal model: Scotland 1980-1999



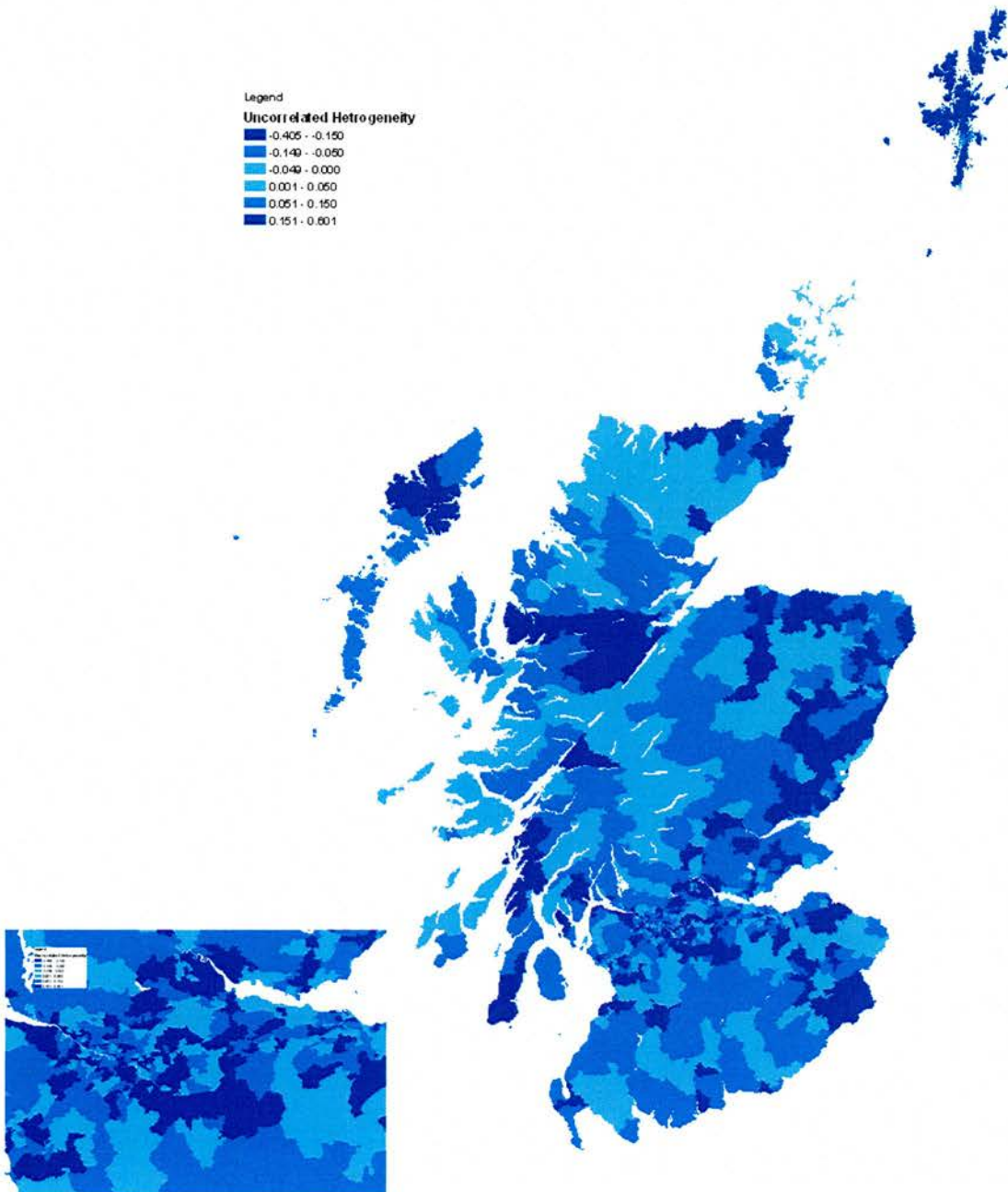
As with the Poisson-Gamma model, the probabilities of the relative risks being greater than 1 show a similar spatial pattern to the relative risks map, so confirming the areas with high and low relative risk while taking into account the variability of the estimates (Figure 40).

**Figure 40** Posterior probabilities of relative risks per 1991 postcode sector for Cryptorchidism from the Log-normal model: Scotland 1980-1999



The uncorrelated heterogeneity term within the Log-Normal model attempts to account for the extra variation of the relative risk estimates. The map of this term by postcode sector will show if there is a spatial clustering of the extra variation (Figure 41).

**Figure 41** Posterior mean uncorrelated heterogeneity term  $v_i$  per 1991 postcode sector for Cryptorchidism from the Log-Normal model: Scotland and Central Belt 1980-1999



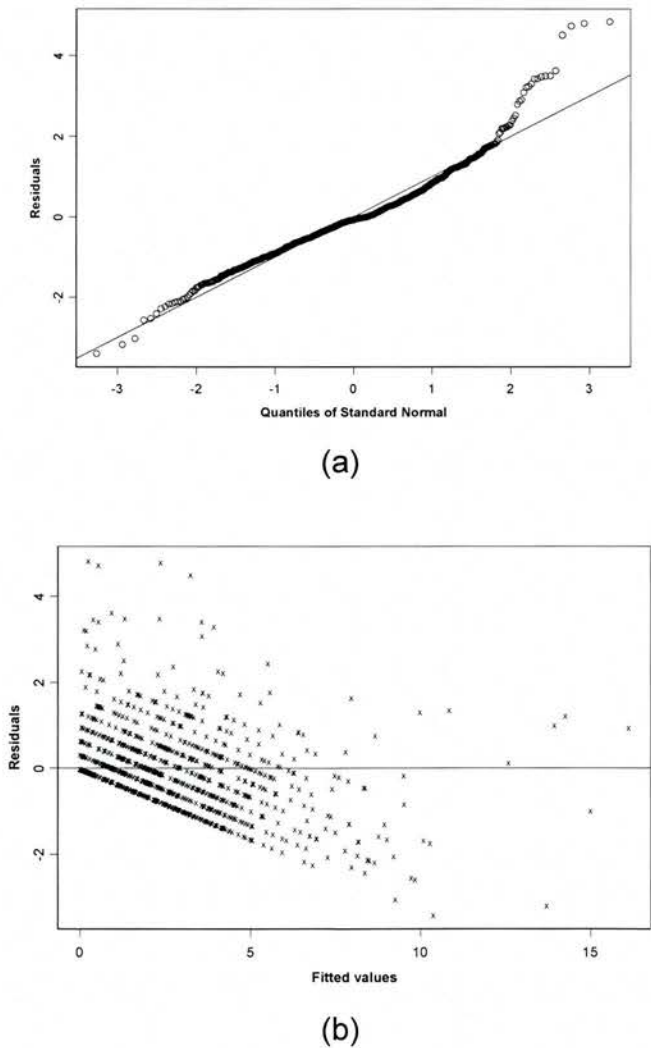


It would appear that those areas with high relative risks also have high extra variation. Therefore the heterogeneity does appear to vary in a spatially structured way, so this term should be included within the model. This is carried out in the BYM model in section 4.6. However, before doing this the residuals of the Log-Normal model need to be fully assessed so as to fully evaluate the model.

4.5.2 Assessment of model

To firstly assess the model an analysis of the residuals is done, as shown in Figure 42.

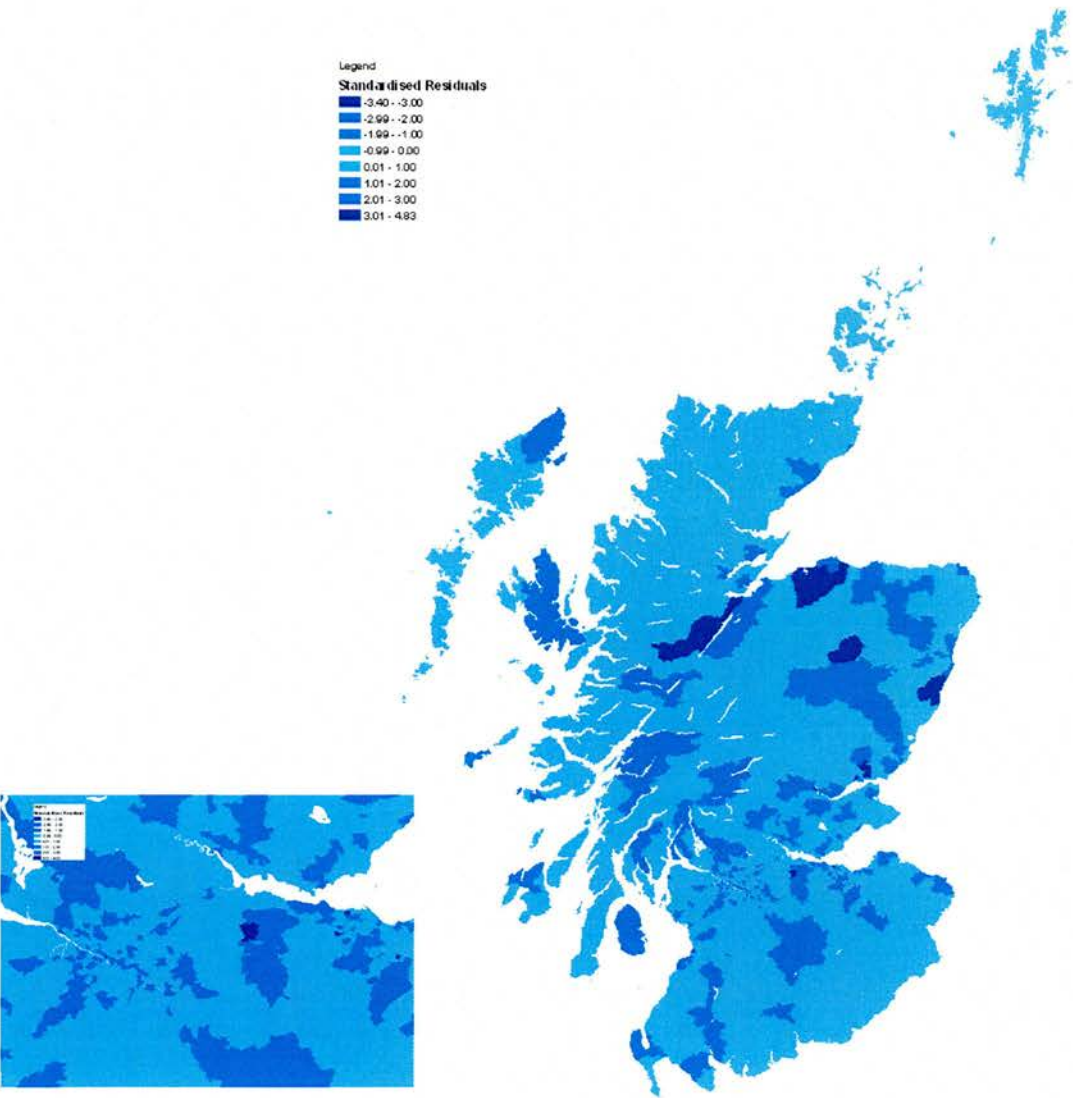
Figure 42 Log-normal Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted



It would appear that the Log-Normal model is not any more successful at fitting the cryptorchidism data than the Poisson-Gamma model. The normal plot (a) shows that although most of the residuals follow the x-y line, the larger extreme values do not fit the Log-Normal model and, as with the Poisson-Gamma model, the residuals are not evenly scattered across all fitted values (b). Therefore, as with the Poisson-Gamma model, the Log-Normal is not a completely successful fit to the cryptorchidism data, particularly for the higher relative risk values.

Figure 43 shows the maps of the residuals produced by the Log-Normal model for each of the postcode sectors.

**Figure 43** Standardised Residuals of Log-normal model for Cryptorchidism: Scotland and Central Belt 1980-1999



As with the Poisson-Gamma model, there might be a spatial correlation of the residual particularly in the North-East of Scotland where the higher relative risks occur. This can be tested formally using the Moran's I (Table 19).

**Table 19** Moran's I test result for residuals from Log-normal model

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.19 (0.15, 0.23)
Correlation Normal p-value (2-sided)	$4.4 \times 10^{-4}$
Mean Permutation correlations (Inter-quartile range)	-0.003 (-0.014, 0.016)
Permutation p-value	<0.00001

As with the Poisson-Gamma model, there appears to statistically significant ( $p = 4.4 \times 10^{-4}$ ) spatial correlation of the residuals, although it is not a strong one ( $r = 0.19$ ). Therefore as the residuals appear to cluster in areas where high relative risks are estimated, then the models does not fully explain the variability of these estimates.

#### 4.5.3 Conclusions for Log-Normal model

The Log-Normal model does not appear to be an improvement on the Poisson-Gamma model for estimating the relative risks for the cryptorchidism dataset. Both show a similar spatial variation of the relative risk of cryptorchidism. However, from the residual analysis of the Log-Normal model it does not appear to fit the cryptorchidism dataset any better than the Poisson-Gamma model. Also from the residual analysis it would appear that there is a spatial component to the heterogeneity of the relative risk estimates.



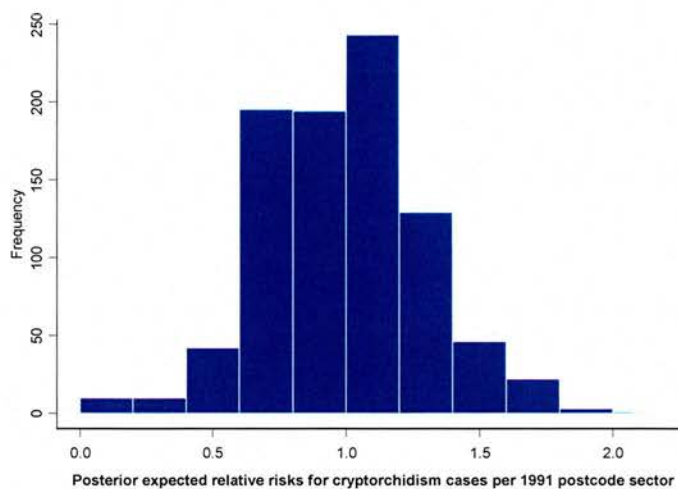
## 4.6 Bayesian Hierarchical Models of cryptorchidism count data - Besag, York and Mollié (BYM) model

As shown in the previous sections neither the Poisson-Gamma nor the Log-Normal models are adequately successful at fitting to the cryptorchidism dataset. While the Log-Normal model includes a random heterogeneity term, neither model takes into account the spatial correlation i.e. that a postcode sector will be similar to its neighbours. It would appear that there is a spatial correlation of the residuals produced by the Poisson-Gamma model residuals and clustering of high relative risks in the North-East of Scotland. The BYM model does include a spatially correlated heterogeneity term. When the model was run in WinBUGs it converged following 10,000 iterations, and a further 20,000 iterations were run to produce robust posterior estimates.

### 4.6.1 Posterior estimates from model

Figure 44 shows the distribution of the posterior expected relative risks estimated from the BYM model. It is similar in shape to the distributions of the relative risks estimated by the Poisson-Gamma and Log-normal models. However the BYM relative risks estimates have a wider range of values ( $1.77 \times 10^{-21}$ , 2.60) compared to the Log-Normal (0.65-1.75) and the Poisson-Gamma models (0.53, 1.8).

**Figure 44** Histogram of Cryptorchidism posterior expected Relative Risk estimated from the BYM model



It is possible to compare the non-postcode-specific parameter estimates produced by the BYM model to those produced by the Log-Normal to see if the inclusion of the spatially correlated heterogeneity term has an impact on the estimates. The population mean relative risk is 0.63 which is considerably lower than that produced by the other Bayesian models and the median SMR (Table 20).

**Table 20** Posterior estimates for non postcode specific parameters in BYM model

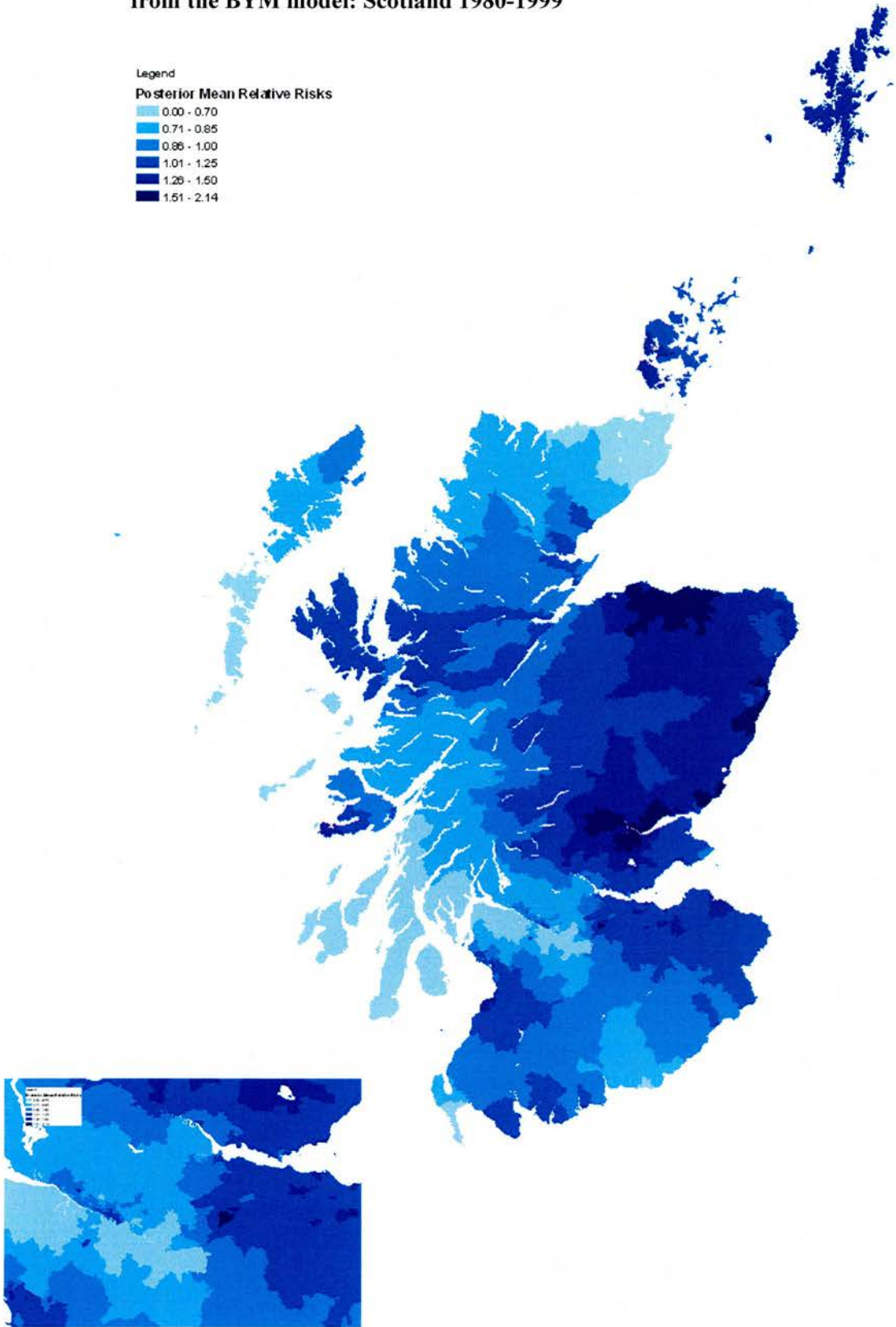
Parameter	Mean	Standard Deviation	MC error	2.5%	Median	97.5%
alpha	-0.4528	0.1079	0.008776	-0.6529	-0.4674	-0.2199
mean	0.6396	0.07019	0.005719	0.5206	0.6266	0.8026
tau.u	5.265	1.005	0.0421	3.64	5.16	7.61
tau.v	1652	1598	123.1	110.3	1114	6046

The intercept term alpha has decreased and the precision of the non-spatial heterogeneity term has deteriorated, compared to the Log-Normal model. Therefore the inclusion of the spatially correlated heterogeneity term appears to have weakened the intercept term and the precision of the non-spatial heterogeneity term.

The maps of the posterior expected relative risks from the BYM model show the same spatial variation as those produced by the other Bayesian models; however it is more distinct (Figure 45). Therefore the inclusion of the spatially correlated heterogeneity term within the model has meant that the relative risk appears to have a more distinct spatial correlation than the other models – higher relative risks in East and South-West of Scotland. This spatial pattern of the relative risks is repeated in the probabilities of the relative risks being greater than 1, therefore confirming the spatial variation of the relative risks produced by the BYM model while taking into account the variability of the estimates (Figure 46).

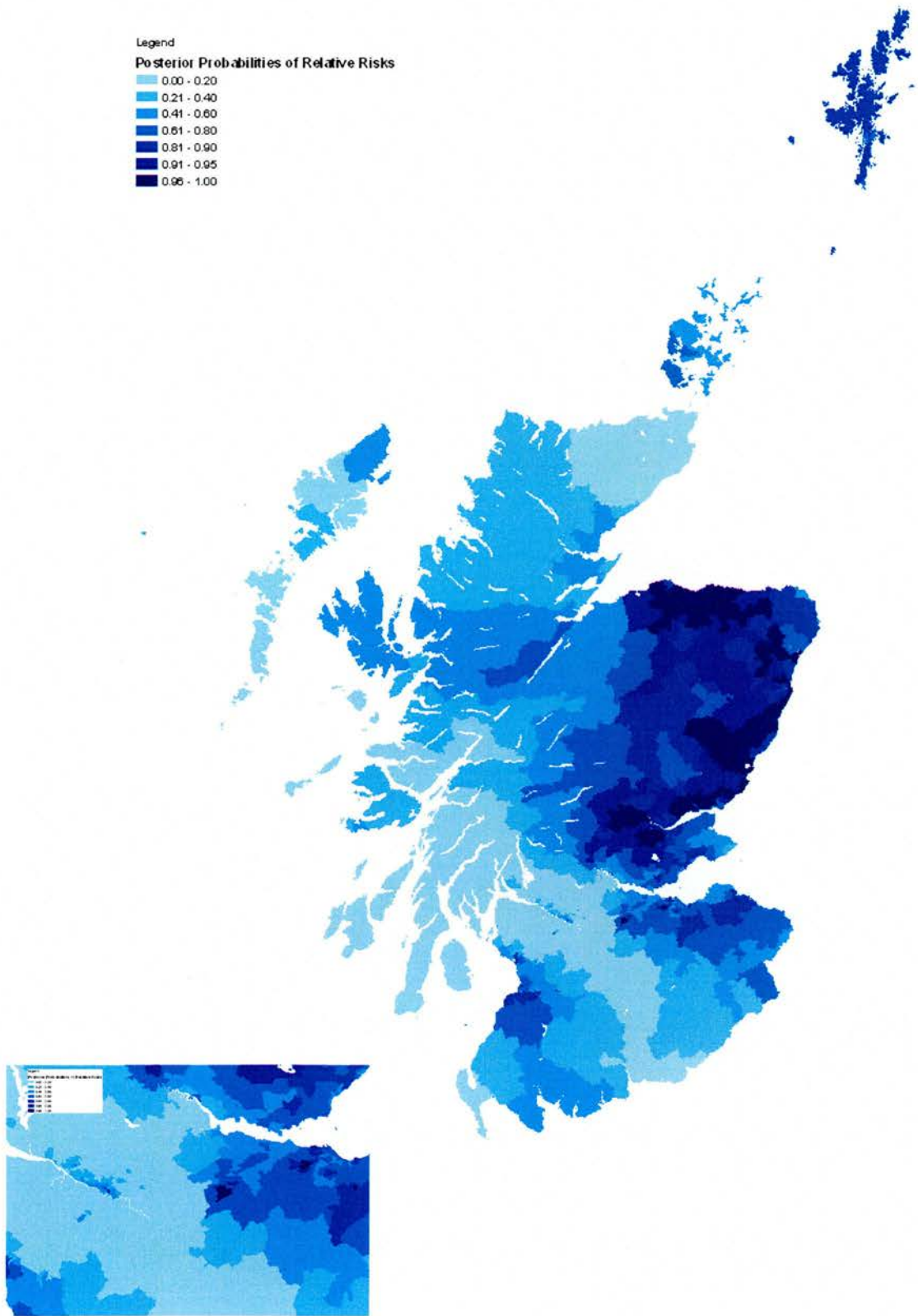
The spatial variation of the heterogeneity terms in the BYM model will show in more detail the heterogeneity of the relative risk estimates. As with the Log-Normal model, the non spatial heterogeneity does appear to have some spatial correlation (Figure 47). The spatially correlated heterogeneity term does show spatial correlation similar to that of the relative risks (Figure 48). Therefore the variability of the random effects appears to have a spatial component.

**Figure 45** Posterior mean relative risk per 1991 postcode sector for Cryptorchidism from the BYM model: Scotland 1980-1999

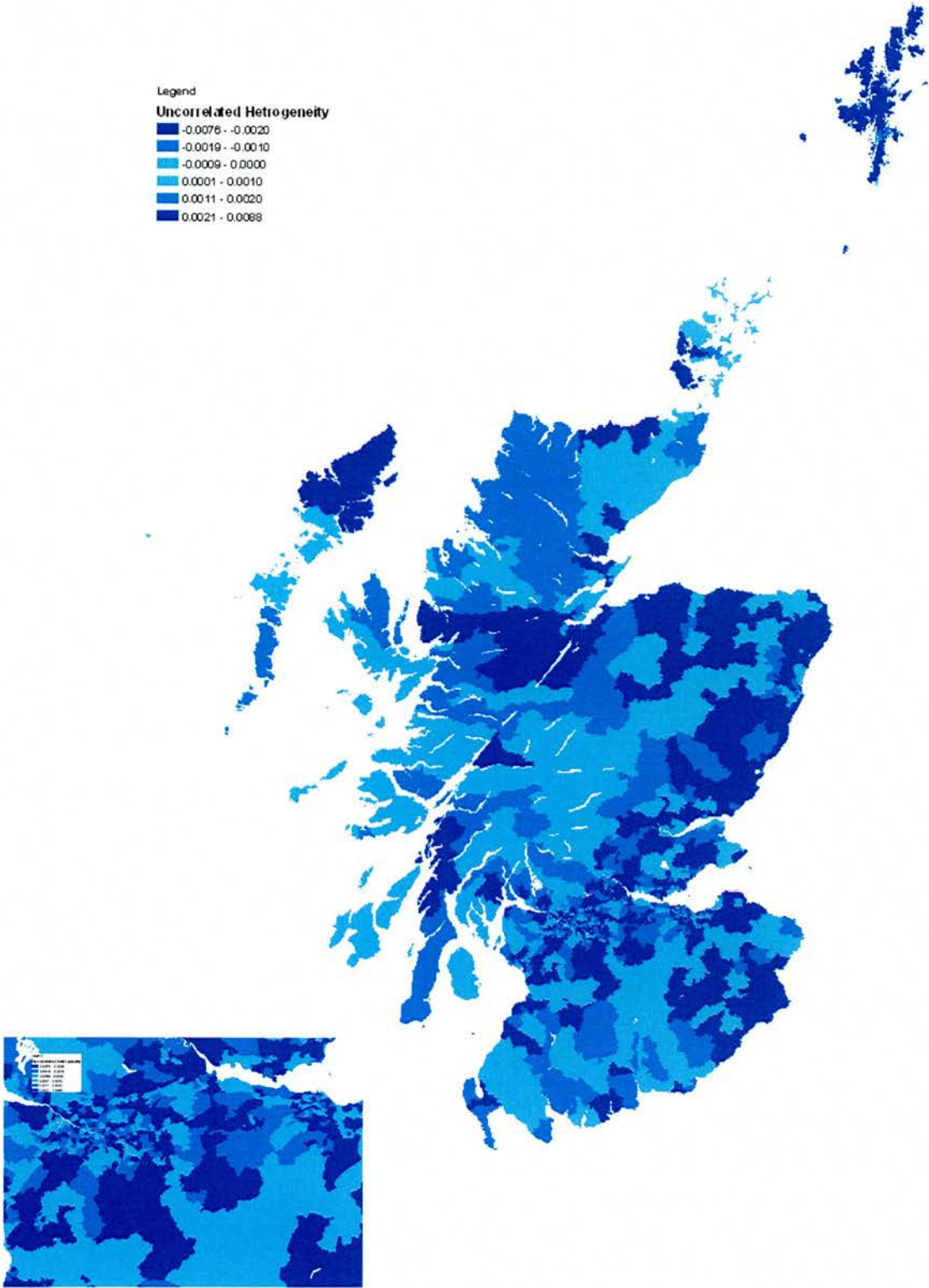




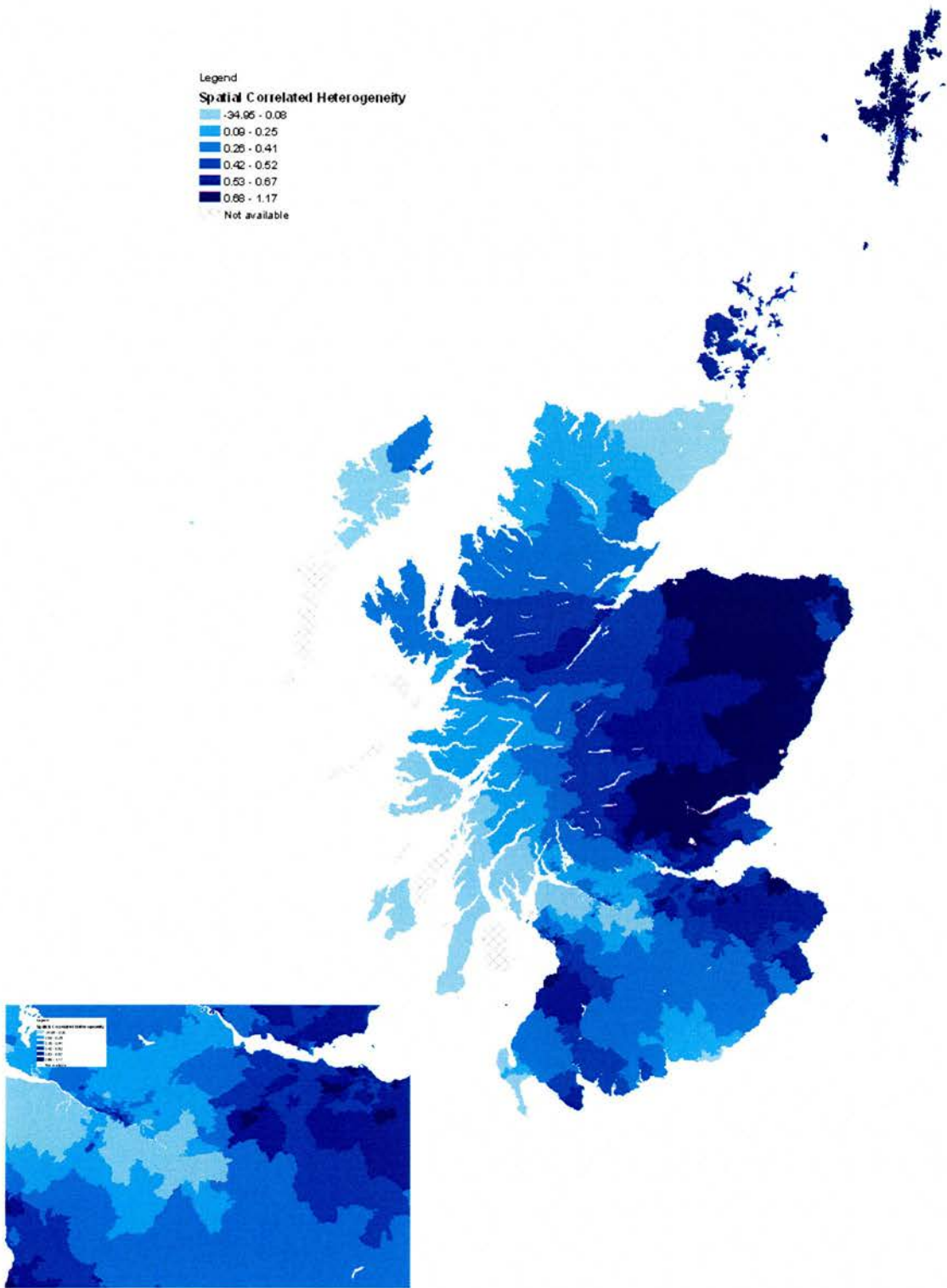
**Figure 46** Posterior probabilities of relative risks per 1991 postcode sector for Cryptorchidism from the BYM model: Central Belt 1980-1999



**Figure 47** Posterior mean uncorrelated heterogeneity term  $v_i$  per 1991 postcode sector for Cryptorchidism from the BYM model: Scotland and Central Belt 1980-1999



**Figure 48** Posterior mean spatial correlated heterogeneity term  $u_i$  per 1991 postcode sector for Cryptorchidism from the BYM model: Scotland and Central Belt 1980-1999





The spatial variation of the heterogeneity terms in the BYM model might be because there is a spatially correlated variability in the estimates of the relative risks. However, it could be that the CAR model used in the BYM model for the spatially correlated heterogeneity term over-smoothes the relative risks and so soaks up all extra variation. This might explain the deterioration in the precision value for the non-spatially correlated heterogeneity term between the Log-Normal and BYM model.

4.6.2 Sensitivity Analysis

As discussed in 3.6.2.4 it was decided to carry out sensitivity analysis on the inverse-variance of the spatial correlated heterogeneity ( $\tau.u$ ) in the BYM model, because of concerns that the spatially correlated heterogeneity term over-smoothes the relative risk estimates.

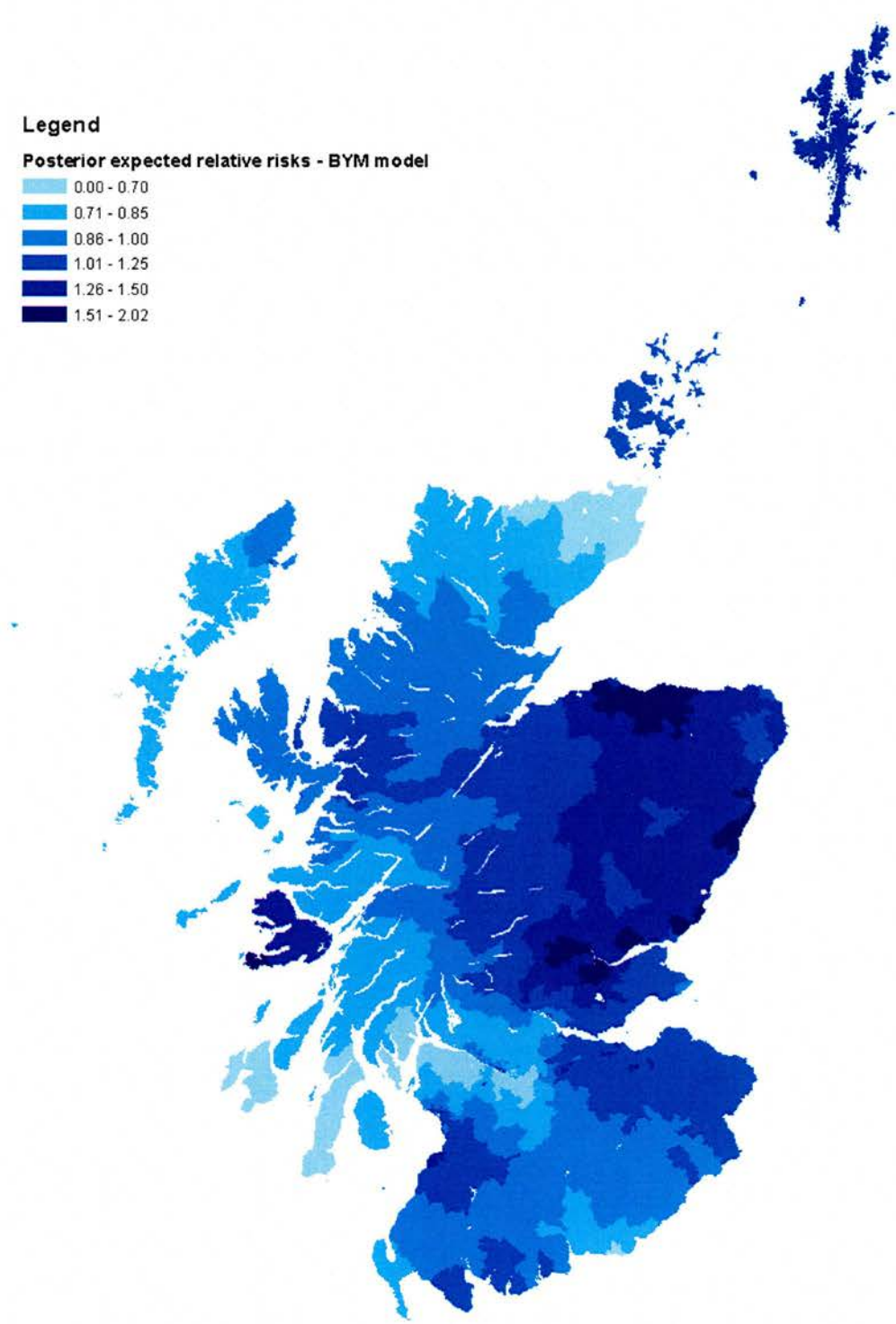
Table 21 shows the results of the comparison of the relative risks estimated by the BYM model outlined (Model 1) and those from the BYM model where the prior for  $\tau.u$  is changed to  $\text{gamma}(0.5, 0.0005)$ . While there appears to be a strong correlation between the two sets of estimated relative risks, those estimated by Model 1 appear to be significantly lower than those estimated from Model 2 for the same postcode sector. However does that change the spatial variation of the relative risks estimated for cryptorchidism?

**Table 21      Comparison tests of Relative Risks estimated from BYM models using prior for  $\tau.u$   $\text{gamma}(1,1)$  (model 1) and  $\text{gamma}(0.5, 0.0005)$  (model 2)**

Correlation co-efficient of relative risks	Mean difference in relative risks (95% CI) (Model 1-2)	Paired t-test – p value
0.989	-0.004 (-0.007, -0.001)	0.0038

If we compare the spatial variation of the relative risks estimated from Model 2 (Figure 49) with those estimated from Model 1 (Figure 46) there is very little difference in the spatial variation of the two. Therefore, while the relative risks estimated by the BYM model with a less specific prior for  $\tau.u$  ( $\text{gamma}(0.5, 0.0005)$ ) are significantly lower than those produced by the BYM model with a more specific prior ( $\text{gamma}(0.5, 0.0005)$ ), this does not alter the distinct spatial variation of the estimated relative risks for cryptorchidism.

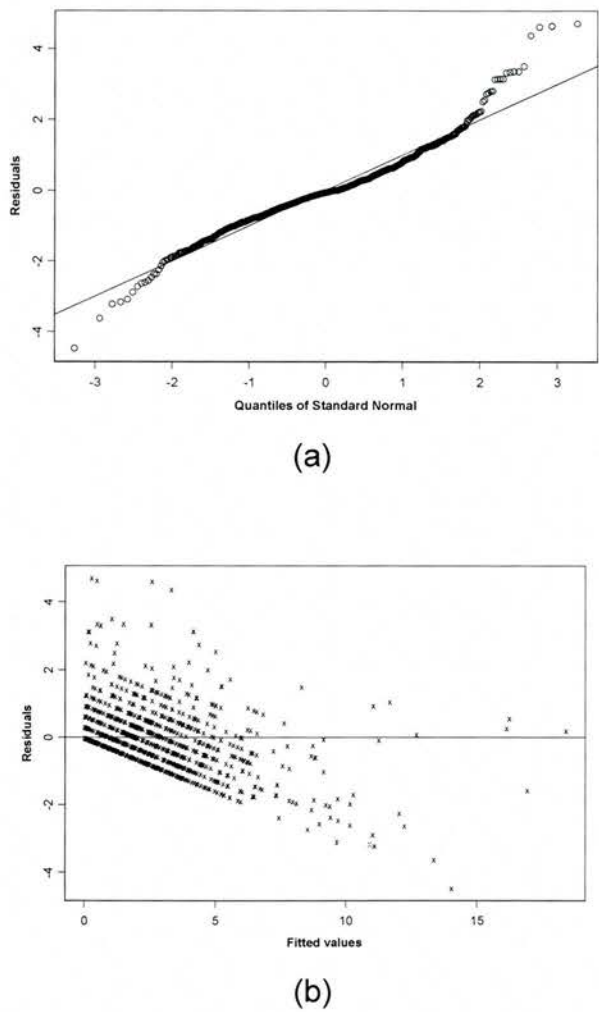
**Figure 49** Posterior probabilities of relative risks per 1991 postcode sector for Cryptorchidism from the BYM model with prior of tau.u gamma(0.5, 0.0005): Central Belt 1980-1999



4.6.3 Assessment of model

An analysis of the residuals of the BYM model might suggest if the BYM model is a better fit of the data and so does the spatially correlated heterogeneity term help model the relative risk estimates (Figure 50).

Figure 50 BYM Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted



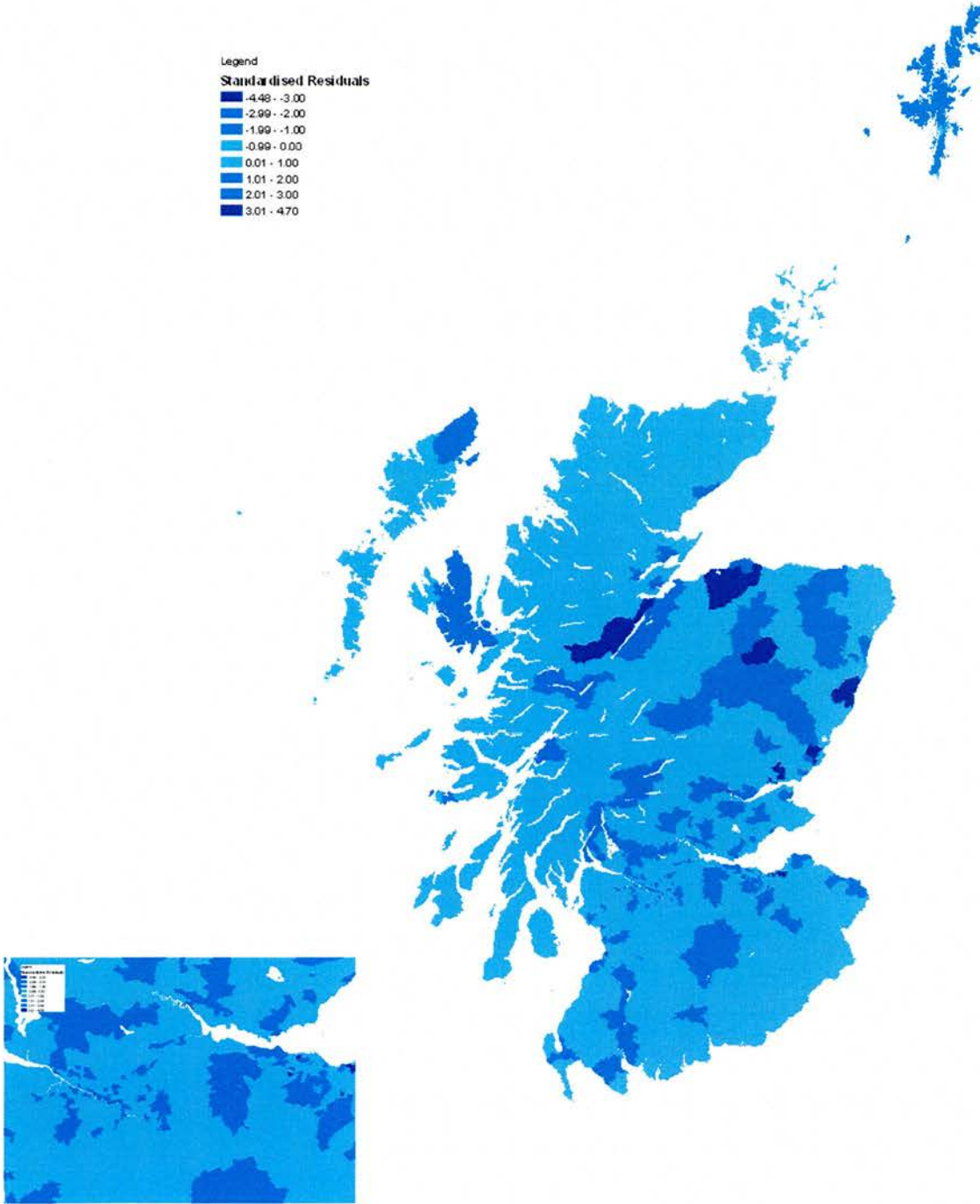
The BYM model is not any more successful at fitting the cryptorchidism data than the other two Bayesian models according to the residual tests. The Normal Plot of the residuals (a) does not follow the  $x=y$  line for the extreme values. As with the other two Bayesian models, the residuals are not evenly scattered when plotted by the fitted values (b), and shows that for the extreme fitted values the models is an



unsuccessful fit. Therefore, as with the other Bayesian models the BYM model is not a complete success at fitting the cryptorchidism data.

From the maps of the residuals, there might again be some spatial correlation in particular in the North-East of Scotland (Figure 51).

**Figure 51** Standardised residuals of BYM model for Cryptorchidism: Scotland and Central Belt 1980-1999



From the Moran’s I test results there is a statistically significant ( $p=8.7 \times 10^{-13}$ ) spatial correlation of the residuals, although it is not strong correlation ( $r=0.15$ ) (Table 22). Therefore as the residuals appear to cluster in areas where high relative risks are estimated, then the model does not fully explain the variability of these estimates.

**Table 22     Moran’s I test result for residuals from BYM model**

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.15 (0.11, 0.19)
Correlation Normal p-value (2-sided)	$8.7 \times 10^{-13}$
Mean Permutation correlations (Inter-quartile range)	-0.004 (-0.019, 0.011)
Permutation p-value	0

As well as comparing residual analysis results, we can compare the three Bayesian models fit to the cryptorchidism data by comparing the DIC diagnostics results (Table 23).

**Table 23     Model fitting results of the three disease count models**

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
Poisson-Gamma model	2856.57	2618.22	238.342	3094.91
Log normal model	2910.16	2711.38	198.777	3108.93
BYM model	2851.36	2720.96	130.406	2981.77

From the deviance  $\bar{D}$ , it would appear that the BYM model is the best fit of the three models. Furthermore it would also appear to be the best model from the DIC results, as this takes into the number of parameters (pD) used within each model. The Poisson-Gamma model is a better model than the Log-Normal model for the cryptorchidism data. Therefore the inclusion of the spatially correlated heterogeneity term within the BYM model compared to the Log-Normal model has greatly improved the fit of the model to the data. Is this because the spatially correlated heterogeneity term is a successful fit to the cryptorchidism data or is this term too successful and ‘soaks up’ all extra variation?

**4.6.4 Conclusions for BYM Model**

Therefore the BYM model appears to produce relative risk estimates that show the spatial variation of the cryptorchidism data more acutely than the other Bayesian

models. Furthermore, in the comparison of the DIC diagnostics it would appear to be the better model in terms of fit to the cryptorchidism data.

However, there are concerns about the performance of the BYM model. The improvement of the BYM compared to the Log-Normal model in terms of the DIC results shows that the inclusion of the spatially heterogeneity term has a considerable impact on the model performance. As already mentioned is this because the spatially correlated heterogeneity term is a successful fit to the cryptorchidism data or is this term too successful and ‘soaks up’ all extra variation. This is not clear from the analysis currently shown.

## **4.7 Inclusion of covariates into Bayesian hierarchical models of disease count data**

None of the Bayesian models have included other covariates that might explain the spatial variation in the relative risks of the cryptorchidism data. Both the Log-Normal and BYM models can include other covariates and as it is unclear of the impact of the spatially correlated heterogeneity on modelling the extra variation, both models have been used in this section to see if the potential covariates explain the variation in the relative risks.

The potential explanatory variables have been described in 3.4.5 and how they were included to the models in WinBUGs is detailed in 3.6.3. These covariates have been included separately to both the Log-Normal and BYM model so as to assess the impact on the inclusion of the covariates with and without the spatially correlated heterogeneity term. Given that the spatially correlated heterogeneity term can soak up any extra variation, then the inclusion of another variable to explain any variation might not be successful.

### **4.7.1 Comparison of Models**

Table 24 shows the different models ran in WinBUGs and the DIC diagnostics results for each. These results are the primary analysis used to assess which model is the most successful at fitting the cryptorchidism data.



**Table 24** Model fitting results of the Bayesian Hierarchical disease count models with covariates

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
1 Poisson-Gamma model	2856.57	2618.22	238.342	3094.91
2 Log normal model	2910.16	2711.38	198.777	3108.93
3 BYM model	2851.36	2720.96	130.406	2981.77
4 Log normal model plus urban/rural indicator	2922.11	2746.22	175.889	3098.00
5 Log normal model plus deprivation (5 groups)	2911.92	2713.14	198.773	3110.69
6 Log normal model plus deprivation (7 groups)	2909.85	2709.26	200.584	3110.43
7 Log normal model plus radon (mean)	2923.39	2763.39	159.999	3083.39
8 Log normal model plus radon (% >200)	2916.86	2741.27	175.592	3092.45
9 BYM model plus urban/rural indicator	2802.45	2592.09	210.365	3012.82
10 BYM model plus deprivation (5 groups)	2798.43	2591.2	207.229	3005.66
11 BYM model plus deprivation (7 groups)	2798.43	2590.55	207.879	3006.31
12 BYM model plus radon (mean)	2800.98	2593.78	207.198	3008.18
13 BYM model plus radon (% >200)	2800.84	2593.86	206.986	3007.83

Comparing deviances  $\bar{D}$  shows that, the log-normal model is not improved, i.e. not a better fit to the cryptorchidism data, for any of the potential covariates that have been included. However from the DIC results, which are the deviances with the number of parameters (pD) is taken into account, the log-normal model fit to the cryptorchidism data is improved by the inclusion of either of the radon measurements and the rural/urban indicator.

According to the deviances  $\bar{D}$  of the various BYM models, the BYM model is improved by the inclusion of any of the potential covariates. However, according to the DIC results none of the BYM models with potential covariates are an improvement on the basic BYM model. Therefore, when the number of parameters is taken into account the fit of the BYM model is not improved by the inclusion of any of the covariates.

The improvement of the Log-Normal model with the inclusion of either of the radon measurements and the urban/rural indicator is not replicated in the BYM models. This difference is probably due to the inclusion of the spatially correlated heterogeneity term within the BYM model soaking up any of the extra variation.

### 4.7.2 Posterior estimates from the models

There is evidence that the spatial variation of the cryptorchidism data is partly explained by the rural/urban indicator and radon measurements of the areas. However, in order to fully assess the models, the posterior estimates of parameters within the models should also be compared so as to indicate which terms within the various models might be explaining the spatial variation in the cryptorchidism risk.

The spatial variations of the relative risks produced by the different Log-Normal models were different dependent on how successful the particular covariate was at improving the model (Figure 52). The deprivation covariates (models 5 and 6) did not improve the Log-Normal model and did not change the spatial variation of the relative risks. Conversely the radon measurement covariates (model 7 and 8) that were the most effective at improving the Log-Normal altered the spatial variation of the relative risks. The maps of the relative risks produced by these two models show more clustering of higher values in the North East of Scotland than in the basic Log-Normal model (model 2). Furthermore, the rural/urban indicator (model 4) which did improve the Log-Normal model, but to not as much extent as the radon measurements has slightly altered the spatial variation of the relative risks. The clustering of the relative risks produced by this model is similar to that of the basic Log-Normal model (model 2). However the values of the areas with the lower relative risks has increased. Therefore, these maps suggest that the radon measurements do explain some of the spatial variation of the relative risks of cryptorchidism and so does the rural/urban indicator to a lesser extent.

Do the BYM models produce the same spatial variation for the different potential covariates? Figure 52 shows the spatial variation of the relative risks for the different BYM models outlined in Table 24. There is very little change in the spatial variation of relative risks between the different models. Therefore the inclusion of potential covariates does not alter the spatial variation of the relative risks of cryptorchidism produced by the BYM model. The differences between Figure 52 and Figure 53 suggest that the spatial heterogeneity term soaks up the extra variation so the inclusion of selected covariates is redundant.



**Figure 52** Posterior Mean relative risks per 1991 postcode sector for Cryptorchidism from the Log-Normal plus covariates: Scotland 1980-1999

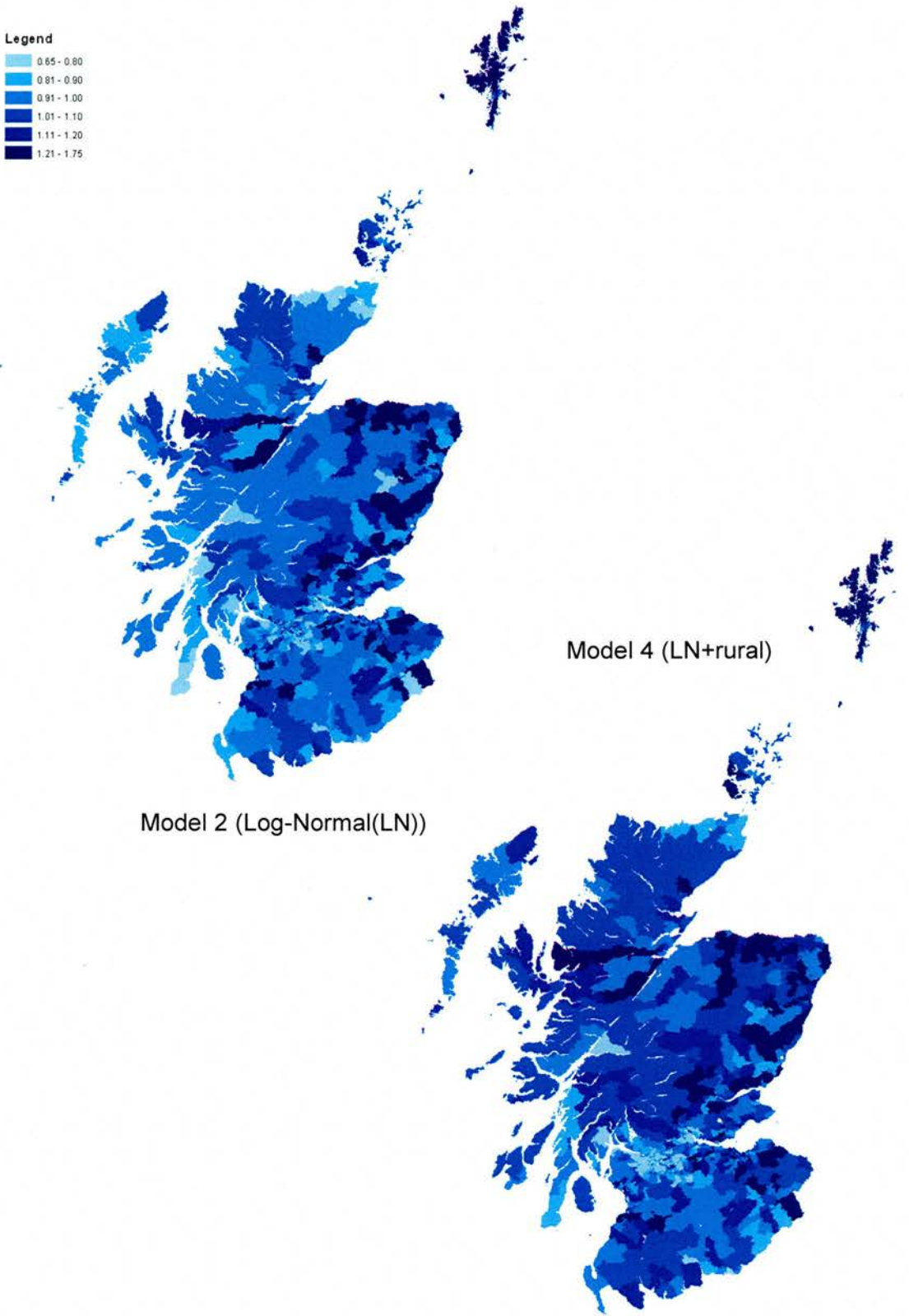




Figure 52 continued

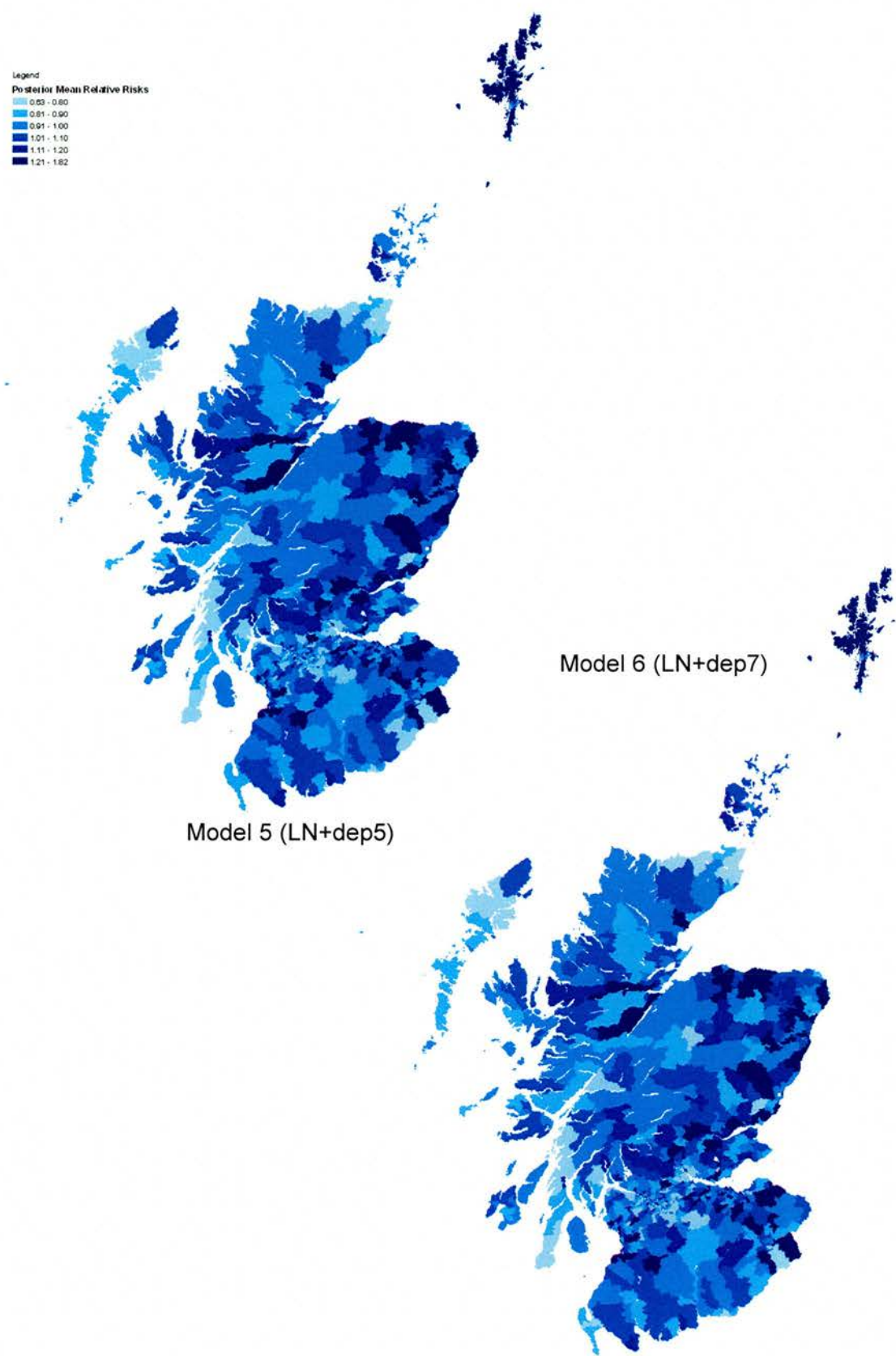
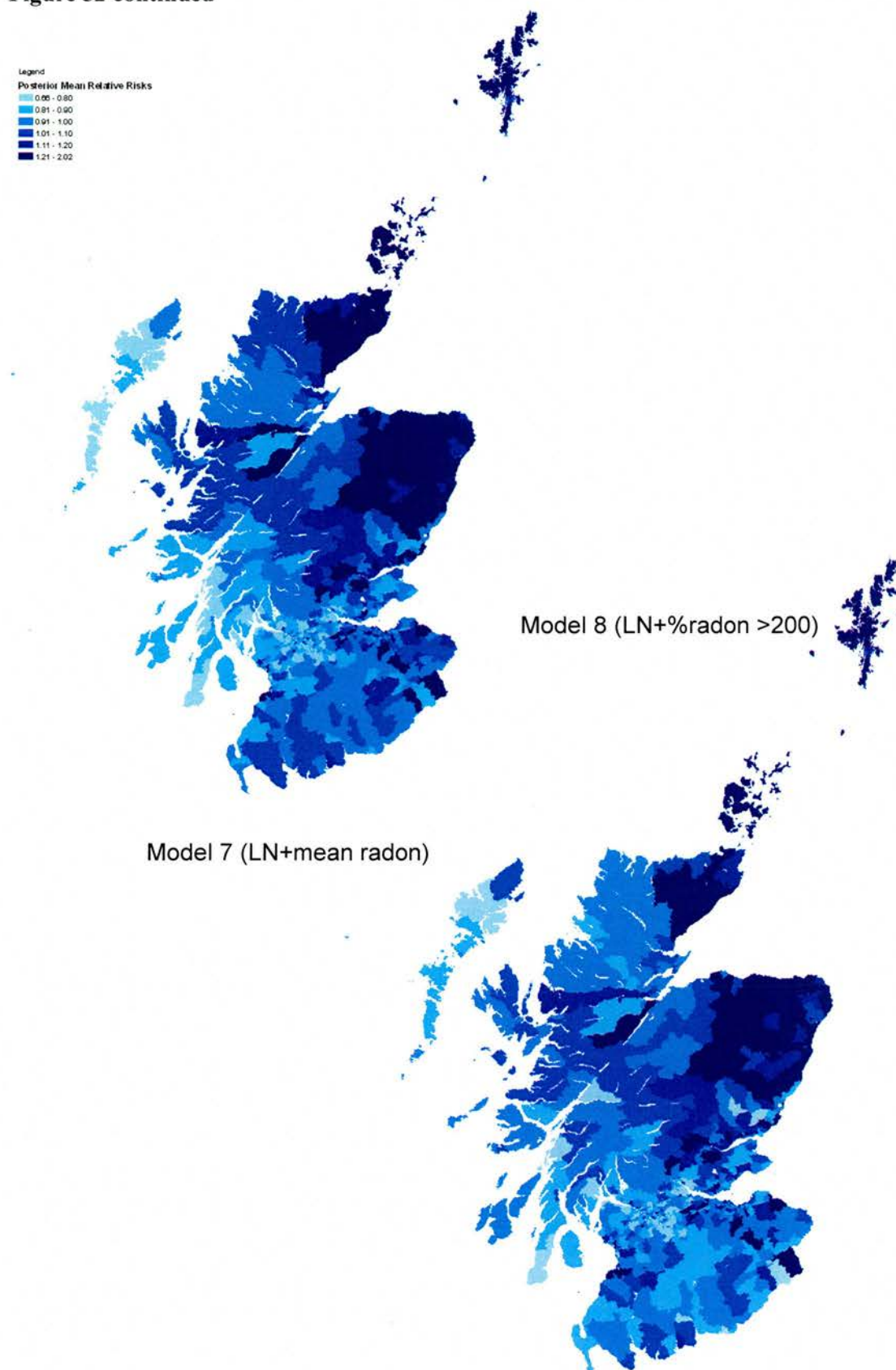


Figure 52 continued



**Figure 53** Posterior Mean relative risks per 1991 postcode sector for Cryptorchidism from the BYM plus covariates: Scotland 1980-1999

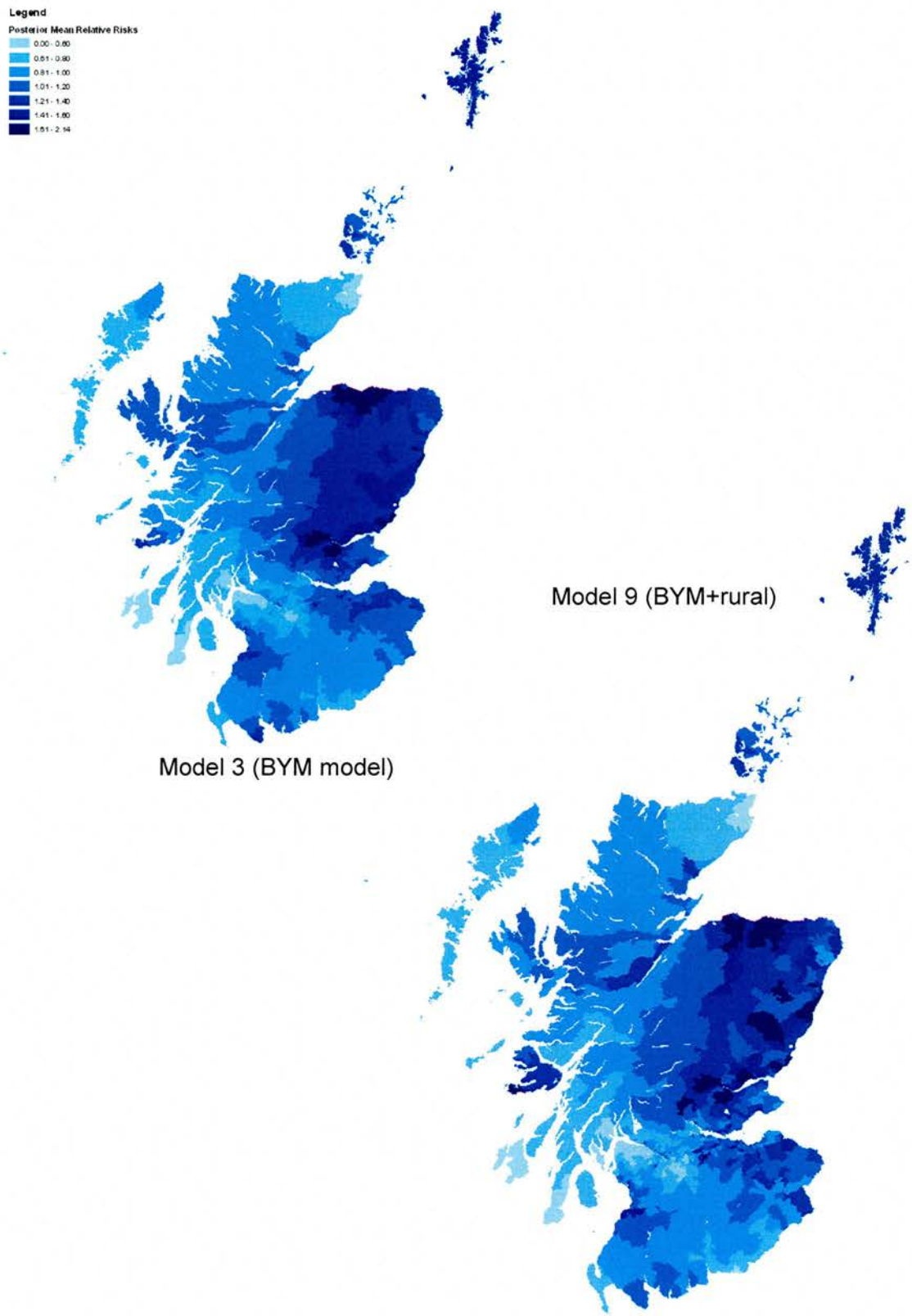




Figure 53 continued

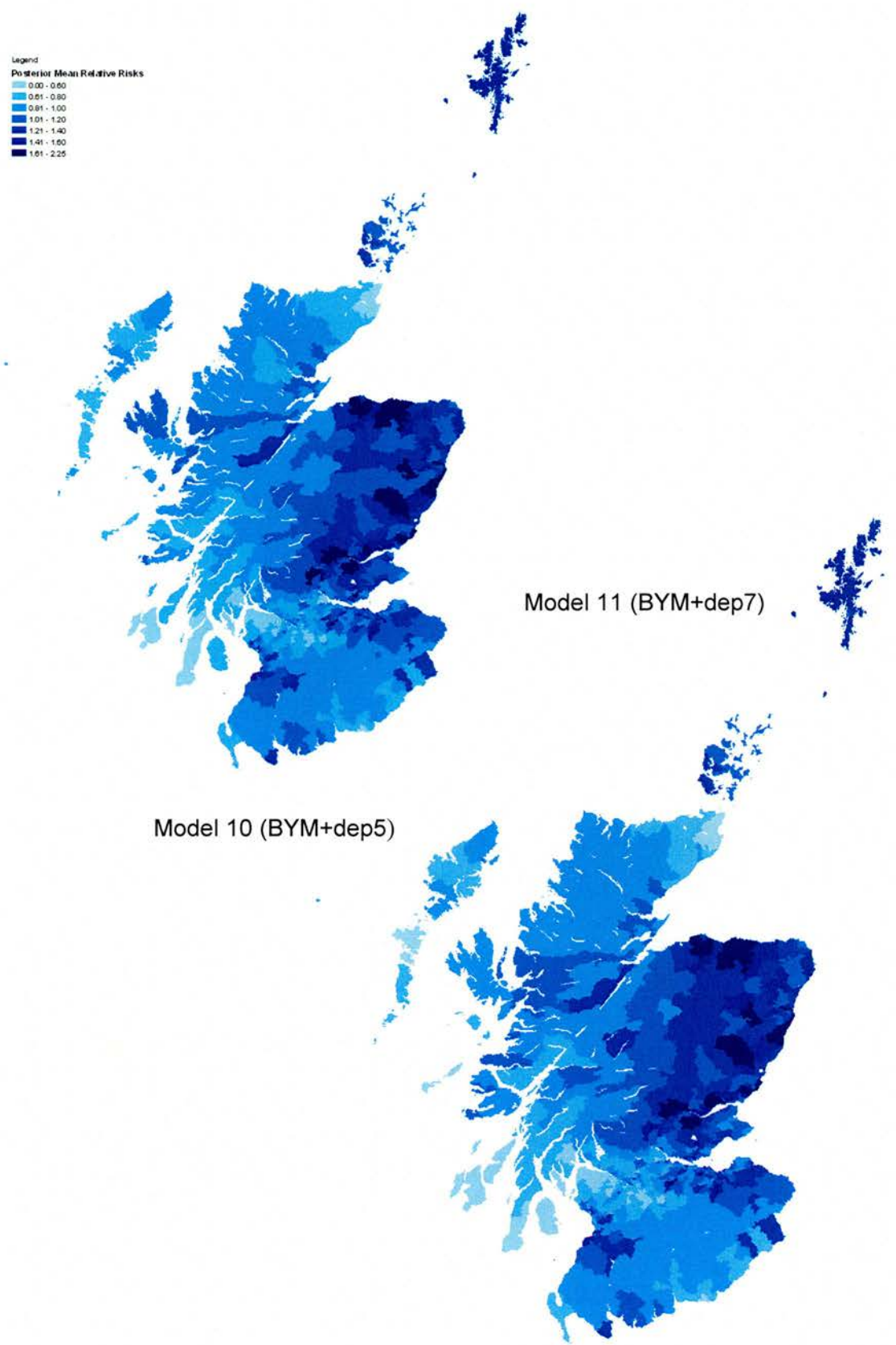
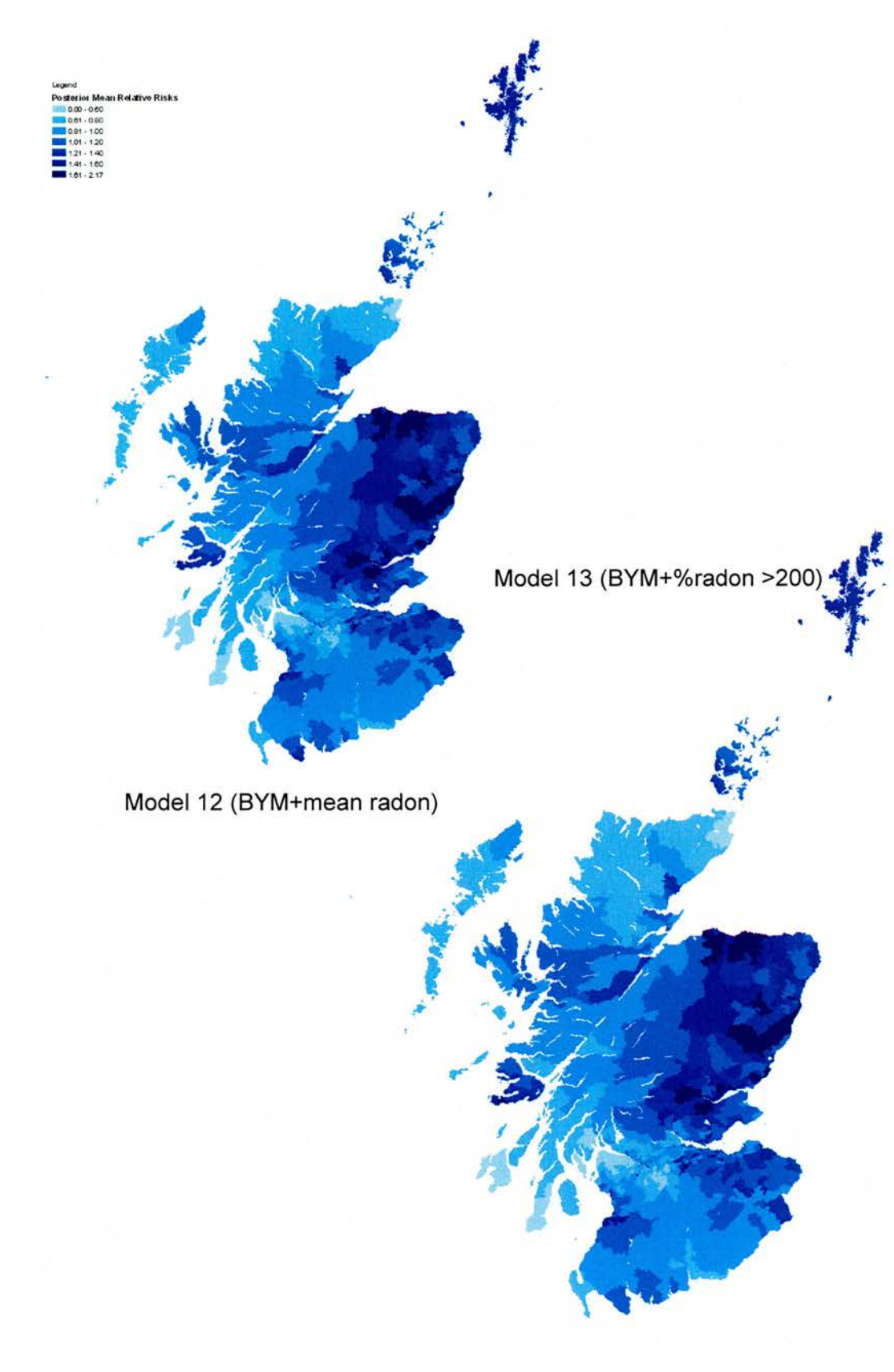
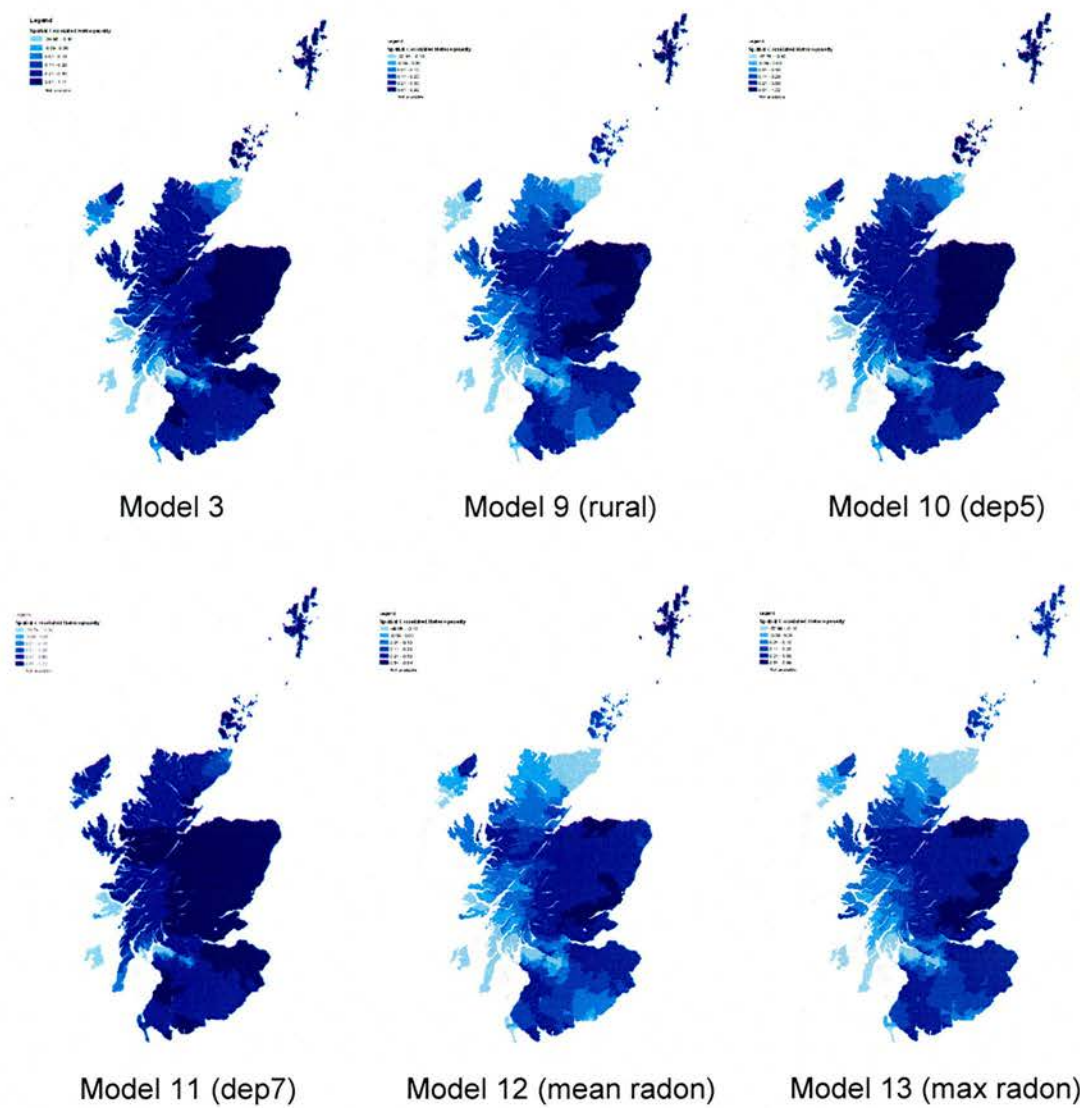


Figure 53 continued



In order to assess if the BYM model is altered by the inclusion of covariates the geographical variation of the spatially correlated heterogeneity term within the models should be compared (Figure 54).

**Figure 54** Posterior Mean Spatial Correlated Heterogeneity term per 1991 postcode sector for Cryptorchidism from the BYM model plus covariates: Scotland 1980-1999



The maps of the spatially correlated heterogeneity term for some of the different BYM models are altered by the inclusion of the potential covariates. For those covariates that did not improve the Log-Normal model (i.e. the BYM without the spatially correlated heterogeneity term) the geographical variation of the spatially correlated heterogeneity term is largely unaltered. However, those covariates that did

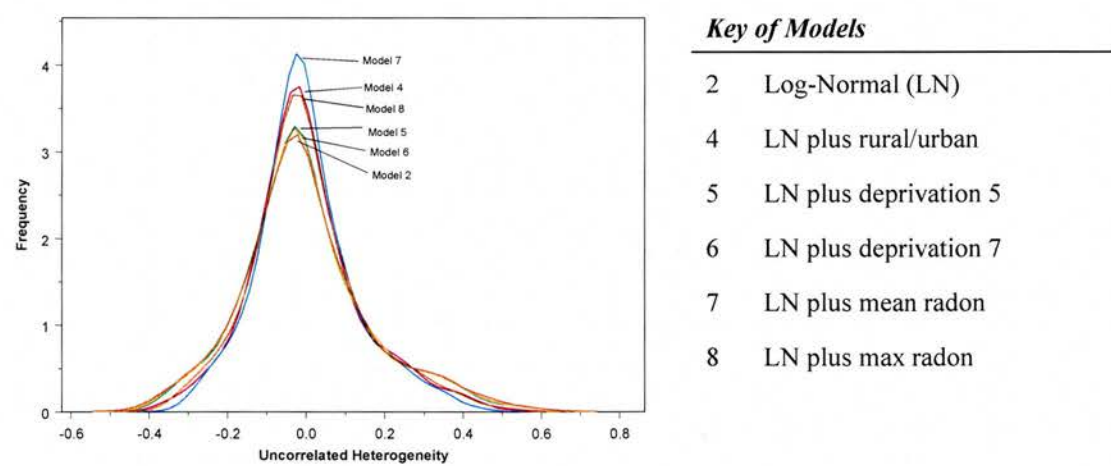


improve the Log-Normal model the most (i.e. the radon measurements – BYM Models 12 and 13) have removed the larger values of the spatially correlated heterogeneity term.

These covariates appear to have accounted for some of the spatially correlated heterogeneity in the BYM model. So there is evidence that the radon measurements and to a lesser extent the rural/urban indicator have been successful at explaining some of the spatial variation of the relative risks in the BYM model, even though this is not underlined by the DIC results. This could be because the spatially correlated heterogeneity term soaks up the extra variation.

Both the Log-Normal and BYM model also have a spatially uncorrelated heterogeneity term. This term may also be affected by the inclusion of potential covariates and so indicate which covariates explain the non-spatial heterogeneity. The distributions of the estimates of the spatially uncorrelated heterogeneity term for the Log-Normal models are shown in Figure 55.

**Figure 55** Posterior Mean Uncorrelated Heterogeneity term per 1991 postcode sector from the Log-Normal model plus covariates: Scotland 1980-1999

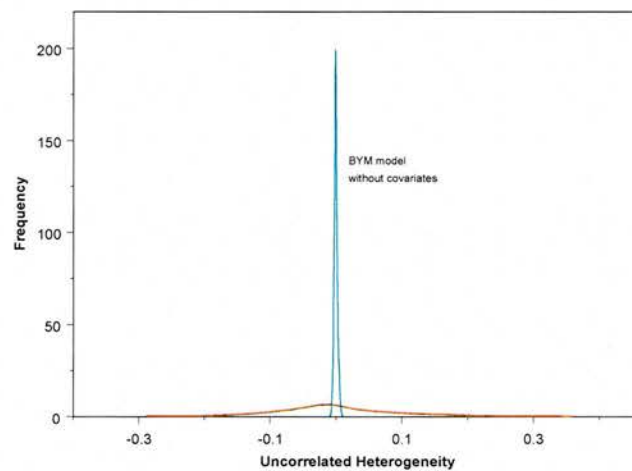


Although very similar, the distributions of estimates of the uncorrelated heterogeneity do alter slightly with the inclusion of the potential covariates. For those covariates (both deprivation terms – models 5 and 6) that did not improve the Log-Normal model the distribution of the spatially uncorrelated heterogeneity term is

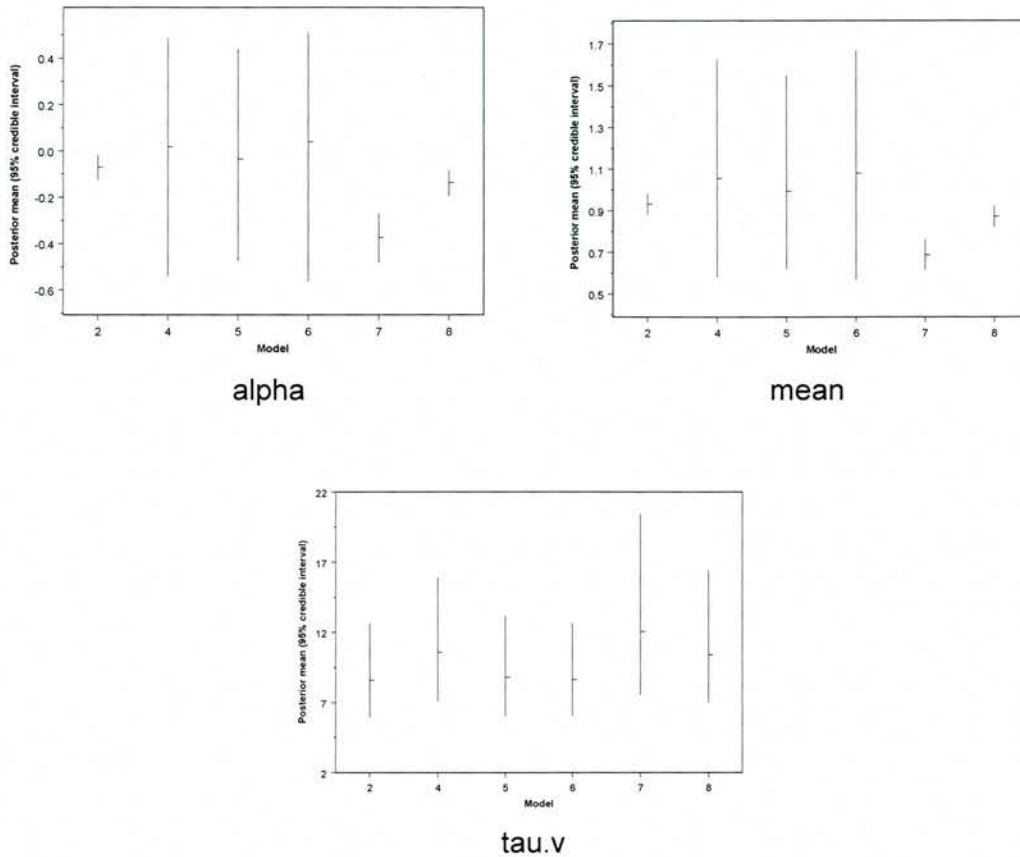
largely unaltered compare to the basic Log-normal model (model 2). Those covariates that did improve the Log-Normal model (i.e. the radon measurements – Models 12 and 13 and the rural/urban indicator – Model 4) have narrowed the distribution of the spatially uncorrelated heterogeneity term. Therefore the inclusion of those covariates that improved the Log-normal model has reduced the non random heterogeneity of the relative risk estimates.

The spatially uncorrelated heterogeneity term was altered by the inclusion of potential covariates to the BYM model to the same degree for model (Figure 56). The distribution of the spatially uncorrelated heterogeneity is widened for all the potential covariates model compared to the basic BYM model. Therefore the inclusion of the covariates to the BYM model has increased the non random heterogeneity of the relative risk estimates

**Figure 56** Distributions of Posterior Mean Uncorrelated Heterogeneity term per 1991 postcode sector from the BYM plus covariates models



Apart from the postcode-specific posterior estimates produced by the models, there are model parameters that might provide more information on how successful the inclusion of potential covariates have been in explaining the spatial variation of the testicular cancer risk. Figure 57 shows the posterior estimates of the parameters for the different Log-Normal models.

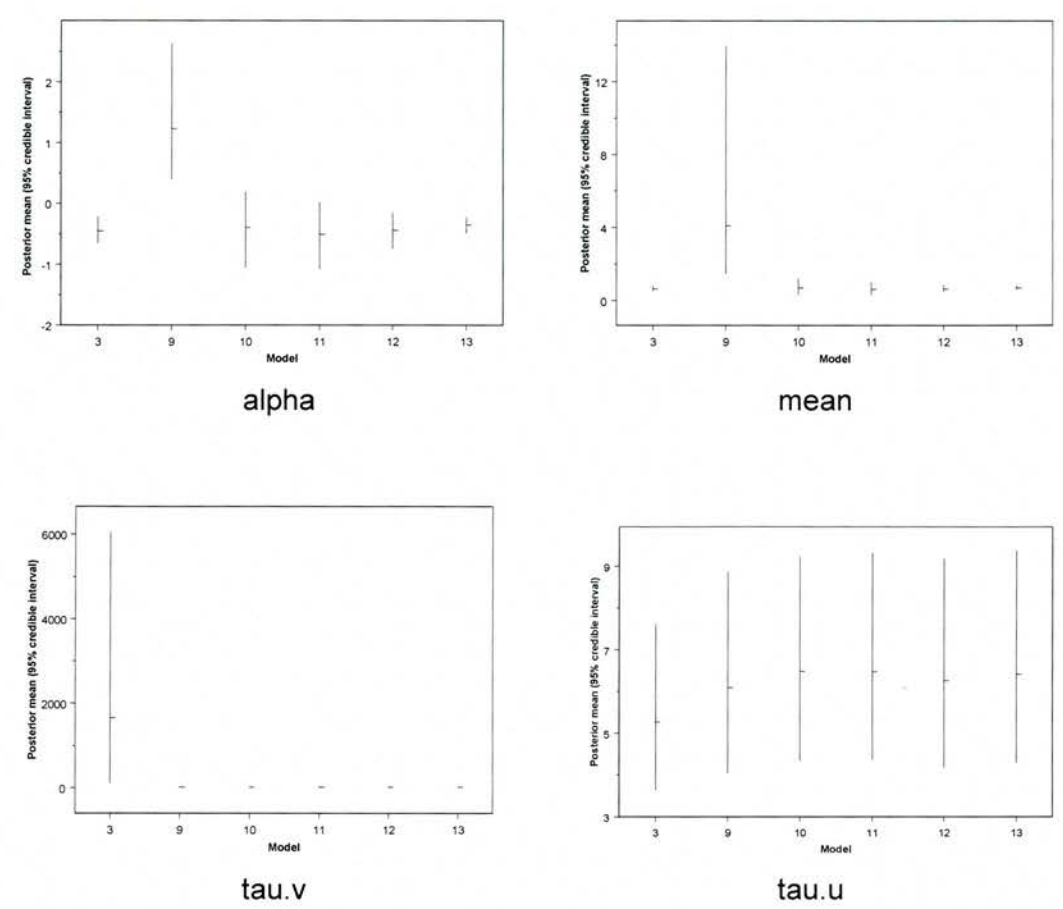
**Figure 57** Posterior estimates for non postcode specific parameters in Log-Normal models

The estimates of the intercept term ( $\alpha$ ) and the population mean relative risk (mean) have been altered in similar ways due to the inclusion of potential covariates to the Log-Normal model. For those covariates that improve the Log-Normal model the most (radon measurements – Models 7 and 8), both terms have been reduced. The  $\alpha$  terms have increased in negative value while the mean term has got closer to zero. The remaining models have produced wider credible intervals on both the  $\alpha$  and mean terms. Therefore any difference between these values and that produced by the Log-Normal model are not conclusive. The estimate of the precision of the uncorrelated heterogeneity ( $\tau.v$ ) is largely unaltered by the inclusion of potential covariates

Do any of these parameter estimates alter with the inclusion of the spatially correlated heterogeneity term? Figure 58 shows the posterior estimates of the non-postcode specific parameters for the different BYM models.



**Figure 58** Posterior estimates for non postcode specific parameters in BYM model



The parameters in the BYM models have been altered differently to those in the Log-Normal models. The intercept term is largely unaltered by the inclusion of the potential covariates except for the model which includes the rural/urban indicator. This model has produced a positive intercept term while the others have a negative value. The population mean relative risk has been altered in a similar way. The model including the rural/urban indicator has increased the population mean relative risk, while the others are comparatively similar. Unlike the Log-Normal models, including the potential covariates has altered the precision of the uncorrelated heterogeneity. The BYM models with covariates have improved the precision of the uncorrelated heterogeneity. Finally, the precision of the correlated heterogeneity is largely unaltered with the inclusion of the potential covariates.

### **4.7.3 Conclusions of Inclusion of Covariates**

Therefore, from the analysis of including covariates into the Log-Normal and BYM model the spatial variation of the cryptorchidism cases can be partly explained by the two radon measurements and the rural/urban indicator. The DIC results for the Log-Normal model show that the model is improved by the inclusion of any of these three covariates. Also, the posterior estimates produced by these Log-Normal models indicate that the spatial variation of the relative risks is partly accounted for and that the heterogeneity of the estimates is decreased. Although the BYM model is not improved by the inclusion of the covariates when comparing DIC results, there is evidence that these three covariates also decrease the heterogeneity of the estimates in the BYM model as with the Log-Normal model.

## **4.8 Individual Level Models**

### **4.8.1 Introduction**

The inclusion of area level covariates into disease count data could have led to ecological bias i.e. associations found at the postcode level could in fact be associations at the individual level. Information about the individual cryptorchidism cases might explain the spatial variation shown.

To assess if information about the individual cases might explain the spatial variation rather than the covariates at the postcode sector, an individual level analysis has been carried out on the cryptorchidism data. As discussed in more detail in 3.7, the spatial distribution of particular individual level information has been modelled to see if they have similar geographical variation as the relative risks of cryptorchidism. If this is the case, it would be suggestive that covariates about the individuals rather than area specific covariates explain the spatial variation in cryptorchidism. If different spatial variation in the relative risks is found in the individual level information, then it would appear that these covariates do not explain the spatial variation of cryptorchidism. However, it does not mean that other individual level information does not explain the spatial variation in cryptorchidism.

Three potential individual level covariates were modelled – co-morbidity, year of birth and age of mother. The models developed and why these covariates were

chosen is detailed in 3.7. The next three sections show the results of the models developed for each covariate.

### 4.8.2 Co-morbidity Models

As shown in 3.4.1 there were babies born diagnosed with cryptorchidism and hypospadias. Of the 2,524 cryptorchidism cases that were geo-referenced to the 1991 postcode sectors, 47 babies were also born with hypospadias.

The logistic regression model developed for the co-morbidity covariate was run with different terms in order to assess which best explains the variation of those cryptorchidism cases. Table 25 shows the different co-morbidity models ran and the corresponding DIC results, where  $v_i$  represents the spatially uncorrelated heterogeneity term and  $u_i$  represents the spatially correlated heterogeneity term.

**Table 25 Co-morbidity Model fitting results**

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
1. Basic model – just beta0 term	469.557	468.590	0.967	470.524
2. Model 1 plus $v_i$	445.668	419.803	25.865	471.533
3. Model 1 plus $v_i$ and x co-ordinates	451.037	423.365	27.671	478.708
4. Model 1 plus $v_i$ and y co-ordinates	463.562	444.996	18.566	482.128
5. Model 1 plus $v_i$ and x and y co-ordinates	397.074	330.266	66.808	463.882
6. Model 1 plus $v_i$ and x and y co-ordinates, and $u_i$	407.026	358.259	48.767	455.793
$v_i$ spatially uncorrelated heterogeneity term				
$u_i$ spatially correlated heterogeneity term				

These changes in the DIC results show that the distribution of those cryptorchidism cases who also have hypospadias is explained with the inclusion of both x and y co-ordinates and the heterogeneity terms.

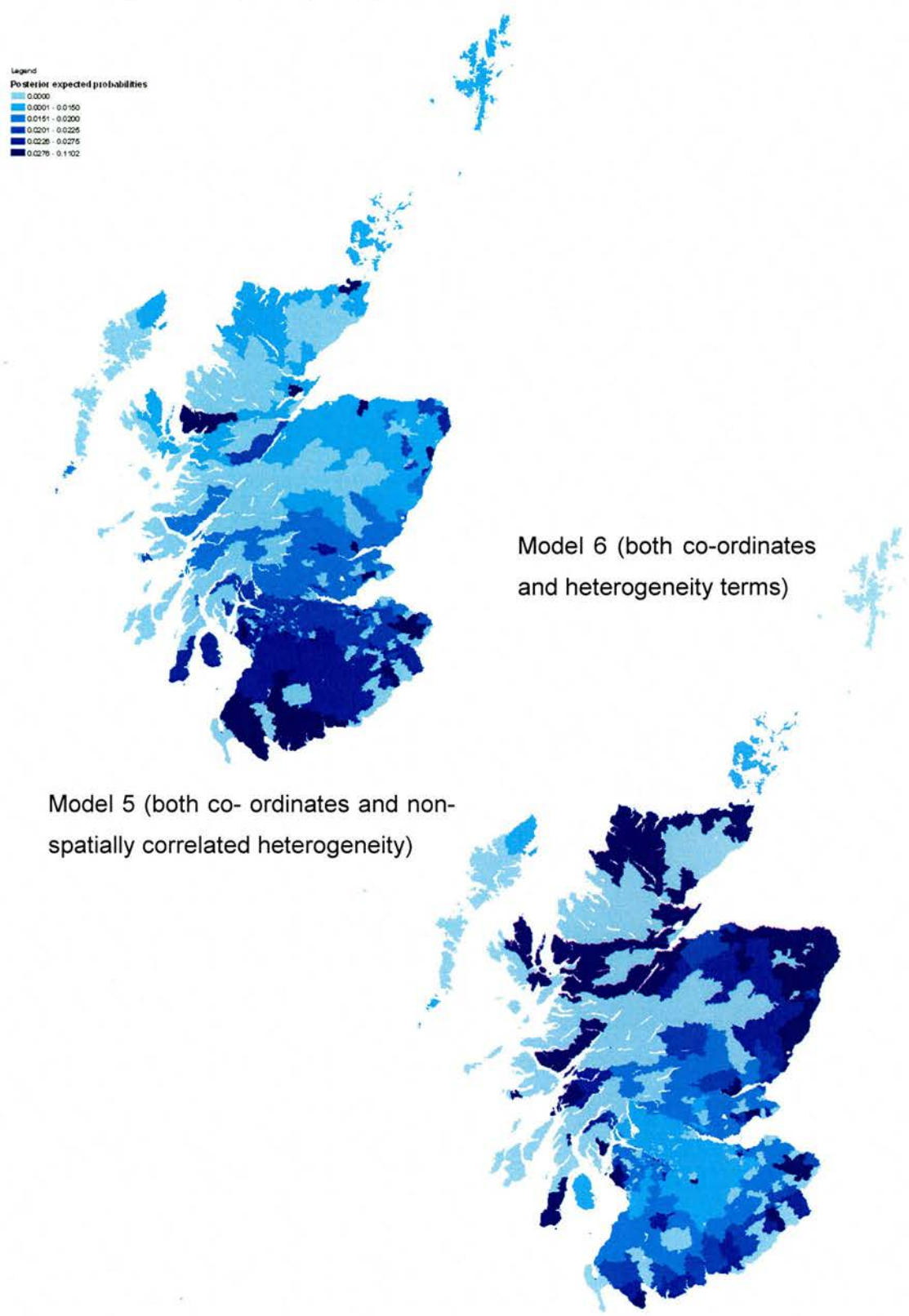
To see if the spatial distribution of co-morbidity is similar to that of the relative risks of the cryptorchidism cases, the posterior estimates of the probabilities produced by models 5 and 6 are looked at in more detail. The probabilities produced by the co-morbidity model give the probability that a particular cryptorchidism case is also diagnosed with hypospadias. The spatial variation of the individual probabilities can be shown by mapping the average probability within a postcode sector. This is calculated by aggregating the individual probabilities to the 1991 postcode sectors and then dividing by the number of individuals within each postcode sector.



The average probabilities per 1991 postcode sector for models 5 and 6 are shown in Figure 59. The spatial distribution of the average probabilities produced by model 5 (all terms except spatially correlated heterogeneity) appear to be the reverse of the cryptorchidism relative risks, i.e. those areas with higher average probabilities of having cryptorchidism and hypospadias cases are those areas with lower relative risks of cryptorchidism. When the spatial correlated heterogeneity term is added to the model (model 6) then the spatial distribution of the average probabilities follows a similar pattern to the relative risks of the cryptorchidism cases. So this map provides some evidence to support the hypothesis that co-morbidity of the cryptorchidism cases may explain their spatial variation. However, there is such difference in the spatial distribution between Models 5 and 6 due to the inclusion of one term. This raises suspicions that this term might over-smooth the relative risks.

In conclusion, the coordinates and the heterogeneity terms explain the distribution of those cryptorchidism cases with hypospadias. Therefore there is a spatial variation to these cases. However, it is inconclusive that the spatial variation of those with both conditions follows the same variation as all cryptorchidism cases. While the probabilities estimated from the model with all the terms found to explain the spatial variation were found to have a similar spatial variation to the cryptorchidism relative risks. The model which excluded the spatially correlated heterogeneity did not have the same spatial variation. Therefore it is uncertain if the co-morbidity explains the spatial variation of the cryptorchidism relative risks. So it is not possible to exclude this covariate from explaining the spatial variation of the cryptorchidism rather than the area-specific covariates therefore the possibility of ecological fallacy is still relevant.

**Figure 59** Average posterior expected probabilities per 1991 postcode sector produced by morphology models 5 and 6



### 4.8.3 Year of Birth Models

The modelling of the year of birth could assess if there is temporal association to the spatial variation of cryptorchidism. As with the co-morbidity model, the polytomous regression model developed for the Year of birth categories was run several times with different terms in each to assess which best explain the variation of the different year of birth groups.

Table 26 shows the different models run and the DIC results.

**Table 26 Year of Birth category Model fitting results**

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
1. Basic model – just beta0 term	6998.010	6998.010	0.000	6998.010
2. Model 1 plus $v_i$	6956.210	6906.010	50.199	7006.410
3. Model 1 plus $v_i$ and x co-ordinates	6883.990	6755.380	128.605	7012.590
4. Model 1 plus $v_i$ and y co-ordinates	6866.910	6724.760	142.146	7009.050
5. Model 1 plus $v_i$ and x and y co-ordinates	6912.440	6807.650	104.792	7017.240
6. Model 1 plus $v_i$ and x and y co-ordinates, and $u_i$	6868.670	6720.650	148.024	7016.700

From comparison of the DIC results, neither coordinates nor the heterogeneity terms improve the model compared to the one with just an intercept term. Therefore, it would appear that the incidence year of the cryptorchidism cases does not have a spatial variation and so unlikely to explain the spatial variation of the relative risks. As this covariate does not appear to have a spatial variation no maps were generated.

### 4.8.4 Age of Mother Models

The age of the mother might explain any spatial variation in cases as previous research has shown that older women have a higher risk giving births to babies with congenital malformations. The different polytomous regression models ran for the Age of Mother categories and corresponding DIC results are shown in Table 27.

**Table 27 Age of Mother Category model fitting results**

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
1. Basic model – just beta0 term	934.240	6934.240	0.000	6934.240
2. Model 1 plus $v_i$	6895.840	6847.450	48.388	6944.230
3. Model 1 plus $v_i$ and x co-ordinates	304.840	1758.270	546.569	2851.410
4. Model 1 plus $v_i$ and y co-ordinates	2304.840	1758.270	546.569	2851.410
5. Model 1 plus $v_i$ and x and y co-ordinates	2305.940	1884.350	421.592	2727.530
6. Model 1 plus $v_i$ and x and y co-ordinates, and $u_i$	2243.210	1723.060	520.147	2763.360



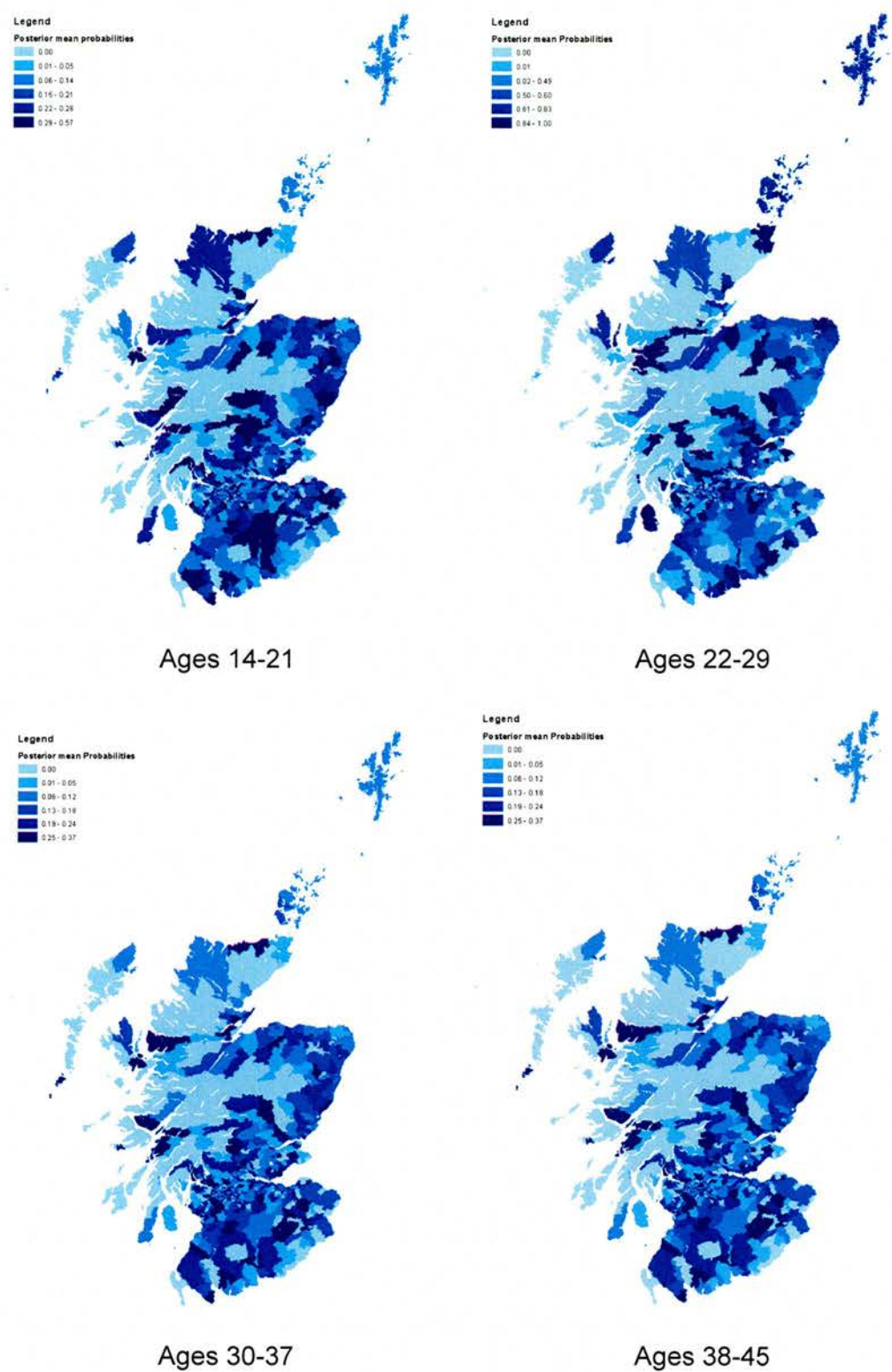
From the comparison of the DIC results the Mother's Age groups do appear to be associated with the coordinates and the spatially uncorrelated heterogeneity term. The spatially correlated heterogeneity term does not appear to improve the Mother Age group model.

To see if the spatial distribution of Mother Age is similar to that of the relative risks of the cryptorchidism cases, the average posterior estimates of the probabilities per postcode sector produced by model 5 are looked at in more detail.

Figure 60 shows the average probabilities for each Age of Mother categories. Unlike previous maps the cut-off values for the categories are different for each Age of Mother group. This is because the aim of each of the maps is to show the spatial distribution of the probabilities within each of the Age of Mother group; and each of the groups has a different range of probabilities.

For all four Age of Mother groups there does appear to be a similarity in the spatial variation of the probabilities and the relative risks for the North of Scotland, i.e. the East has high probabilities while the West has low probabilities. However, the spatial variation of the probabilities in the South of Scotland does not show the same spatial variation as estimated for the relative risks. Therefore, these maps suggests that the age of the mother might partly explain the occurrence of the cluster of high relative risks in North East Scotland but does not explain the region of low relative risks in the South of Scotland.

**Figure 60** Average posterior expected probabilities per 1991 postcode sector produced model 5 by Mother's Age Category



The differences in the range of probabilities between the four Mother of Age groups gives an insight into the role of this covariate in explaining the variation of the relative risks of cryptorchidism. Those women in the two older age groups have the lower range of probabilities, which contrary to previous research, appears to indicate that the cryptorchidism cases are less likely to be born to these women. Those women in the two younger age groups have a higher range of probabilities; in particular those women aged 22 to 29. So it would appear that the cryptorchidism cases are more likely to be born to younger women, in particular those women in their 20's.

In conclusion, the co-ordinates and the non-spatially correlated heterogeneity explain the variation in the cryptorchidism cases by Age of Mother group. Therefore the grouping of cryptorchidism cases by Age of Mother does have a spatial variation. Furthermore, the spatial variation of the probabilities of being in these groups is similar to the cryptorchidism relative risks in the North of Scotland. This similarity in spatial variation suggests that the age of the mother might partly explain the occurrence of the cluster of high relative risks in North East Scotland but does not explain the region of low relative risks in the South of Scotland. Finally the differences in probability values between the four Age of Mother groups suggests that the cryptorchidism cases are more likely to be born to younger women, in particular those in their 20's.

#### **4.8.5 Conclusions for Individual Models**

From the individual models it would appear that the spatial variation of the cryptorchidism cases could also be explained by information known about the individual cases. Therefore the presence of ecological bias cannot be ruled out in the disease count models. From the individual analysis, the age of the mother is associated with the spatial variation of the cryptorchidism relative risks. The comorbidity of hypospadias for the cryptorchidism cases may also explain the spatial variation although it is not conclusive.



## 4.9 Summary of Cryptorchidism Analysis

There does appear to be a spatial variation in the cryptorchidism cases, with a cluster of high relative risks in the North-East and generally lower relative risks in the South and West. Although this spatial variation was shown by all three Bayesian Hierarchical models, each had varying success at fitting the data.

Both the Poisson-Gamma and Log-Normal model smoothed the relative risks towards the overall mean and so decreased the range of their values. From the comparison of the DIC results the Poisson-Gamma was actually a better fit to the cryptorchidism data, although neither fully accounted for the variability of the relative risk estimates. From the residual analysis, neither model was successful at fitting those postcode sectors with high relative risks. Furthermore, the residuals produced by both models appear to show some spatial correlation, so there is evidence that there is a spatial component to the heterogeneity of the cryptorchidism relative risk estimates.

The BYM model did include a spatially correlated heterogeneity term and, in the comparison of the DIC results, it would appear to be the better model in terms of fit to the cryptorchidism data. However concerns were raised from the analysis about the performance of the BYM model. The residual analysis did not show an improvement on the other two models and there was still spatial correlation of the residuals.

Furthermore, two other outcomes of the BYM model mean it is unclear if the spatially correlated heterogeneity term explained the relative risk estimates variation, or that this term over-smoothes this heterogeneity. Firstly, the relative risk estimates produced by the BYM model show a considerably more distinct spatial variation of cryptorchidism than those produced by the other two Bayesian models. It is surprising to see such a difference in the Log-Normal and BYM models results, only due to the inclusion of the spatially correlated heterogeneity. Secondly, the sizable improvement of the DIC results for the BYM compared to the Log-Normal model, shows that the inclusion of the spatially heterogeneity term has a considerable impact on the model's performance.

With the cryptorchidism cases showing a spatial pattern, can the inclusion of possible area-specific covariates explain this variation? From the analysis of including covariates into the Log-Normal and BYM models the spatial variation of the cryptorchidism cases can be partly explained by the two radon measurements and the rural/urban indicator. The DIC results for the Log-Normal models show that the model is improved by the inclusion of any of these three covariates. Furthermore, the posterior estimates produced by the Log-Normal models including these covariates indicate that the spatial variation of the relative risks is partly accounted for and that the heterogeneity of the estimates is decreased.

Although the BYM model is not improved by the inclusion of any of the covariates, when comparing DIC results, there is evidence that the same three covariates decrease the heterogeneity of the estimates in the BYM model as with the Log-Normal model. The difference in conclusions made from the DIC diagnostics and the heterogeneity estimates could be because the spatially correlated heterogeneity term is ‘soaking up’ any extra variation, so making the inclusion of potential covariates redundant within the BYM model.

From the individual-level models the presence of ecological bias cannot be ruled out in the Bayesian Hierarchical disease count models of cryptorchidism. The spatial variation of the cryptorchidism cases could be explained by information known about the individual cases. In particular, the individual models were able to show that the age of the mother is associated with the spatial variation of the cryptorchidism relative risks. There is also evidence that the co-morbidity of hypospadias for the cryptorchidism cases may also explain the spatial variation although it is not conclusive. As will be discussed in more detail in Chapter 8 this individual analysis only indicates if the individual level information might explain the spatial variation of the cryptorchidism cases rather than showing direct relationships. The individual level analysis was done to explore if there was a possibility of ecological fallacy in the disease count models.



## **Chapter 5 : Testicular cancer Analysis**

### **5.1 Introduction**

This chapter details the analysis of the testicular cancer dataset. The testicular cancer data has been analysed as disease count data and uses the same methods outlined for the cryptorchidism data in sections 4.3-4.7. Therefore the methods are not described in this chapter and the reader is referred to the previous chapter for further explanation of the analysis.

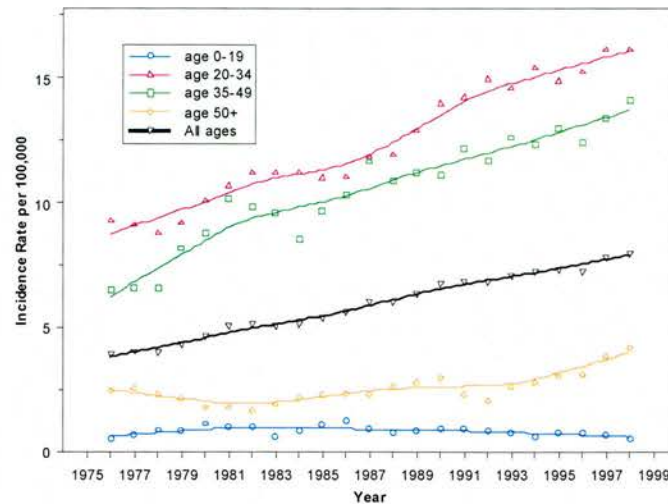
### **5.2 Incidence over time**

Unlike the cryptorchidism chapter there has not been a spatial analysis of the individual level covariates. Therefore, the only summary of the variables included in the testicular cancer data (further details Appendix 2) is the temporal changes of incidence. This was included as the proposed environmental factor being associated with testicular cancer stem from reported increases over time in particular conditions/diseases, including testicular cancer. Unless this is found in the three disease/conditions datasets, then the environmental exposure might not have occurred in Scotland. It would appear that the increase in the incidence of testicular cancer has occurred in Scotland (Figure 61). Furthermore, there also appears to be differences in the incidence and rate of increase of incidence between age groups, which correspond with previous data outlined in 2.2.1.

The age groups with the highest incidence (20-40) correspond with previous research, and show the greatest increase in incidence over time. Those that are in the youngest age group have the lowest incidence and also show relatively little change in incidence over time. Those that are in the oldest age groups have a slightly higher incidence than the youngest age group and show some increase over time in incidence. If individual level models were to be developed for the testicular cancer data it would appear that age at incidence might be one to investigate further.



**Figure 61 Annual incidence rate by age group for testicular cancer in Scotland (3 year moving average)**



### 5.3 Standardised Morbidity Ratio (SMR) maps

The following gives the results of these calculations in relation to the testicular cancer dataset.

#### 5.3.1 Observed number of testicular cancer cases per 1991 postcode sector

Of the 3,624 cases of Testicular Cancer, 5 did not have postcode sector recorded. The remaining 3,619 cases were linked to the database created that matches all valid postcode sectors to where this would have been in 1991. All these 3,619 cases were successfully linked to a 1991 postcode sector.

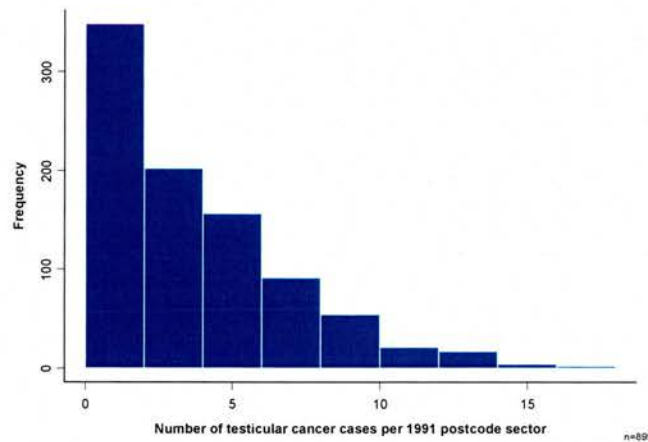
The distribution of the number of cases within each of the postcodes sectors is shown in Figure 62. As can be seen from the figure, the distribution is highly skewed - the number of cases in each postcode sector ranges from 0 to 18 with a median of 3 cases.

#### 5.3.2 Expected number of Testicular Cancer cases per 1991 postcode sector

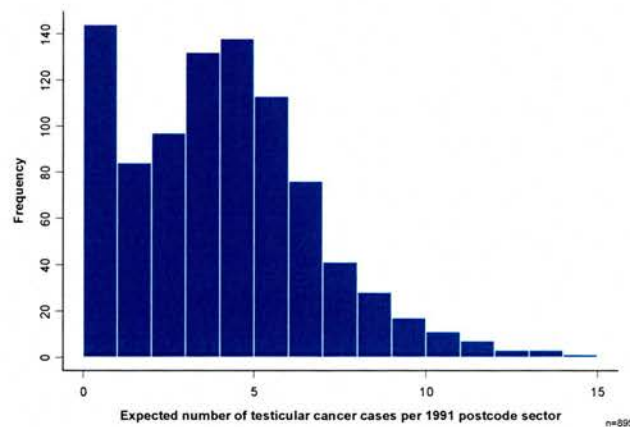
The expected numbers of Testicular Cancer cases per 1991 postcode sector were standardised by age and the underlying population used was the Census 1991 population. The distribution of the expected number of Testicular Cancer cases within each of the 1991 postcode sectors is also skewed Figure 63. The distribution

appears to be not as skewed as that for the observed cases per postcode sector. While the range of values is less (0-15), the median expected value is larger (3.96) and the mean numbers of cases per postcode sectors are similar (4.05 expected; 4.04 observed).

**Figure 62** Histogram of the number of Testicular Cancer cases per 1991 postcode sectors



**Figure 63** Histogram of the expected number of Testicular Cancer cases per 1991 postcode sectors



### 5.3.3 SMRs of Testicular Cancer per 1991 postcode sector

The distribution of the Testicular Cancer SMRs for the 1991 postcode sectors is skewed; the maximum SMR is 18.9 while the third quartile is 1.32 (Figure 64). The mean SMR is 1.02 (standard deviation 3.4) and the median is 0.92. There is no strong evidence of spatial clustering of the testicular cancer SMRs across Scotland (Figure 65).

Figure 64 Histogram of Testicular Cancer SMRs per 1991 postcode sector

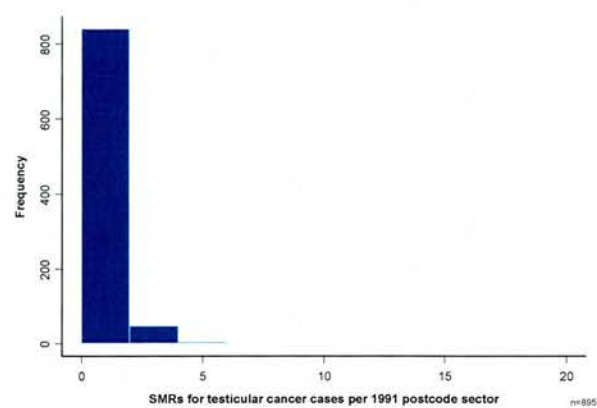
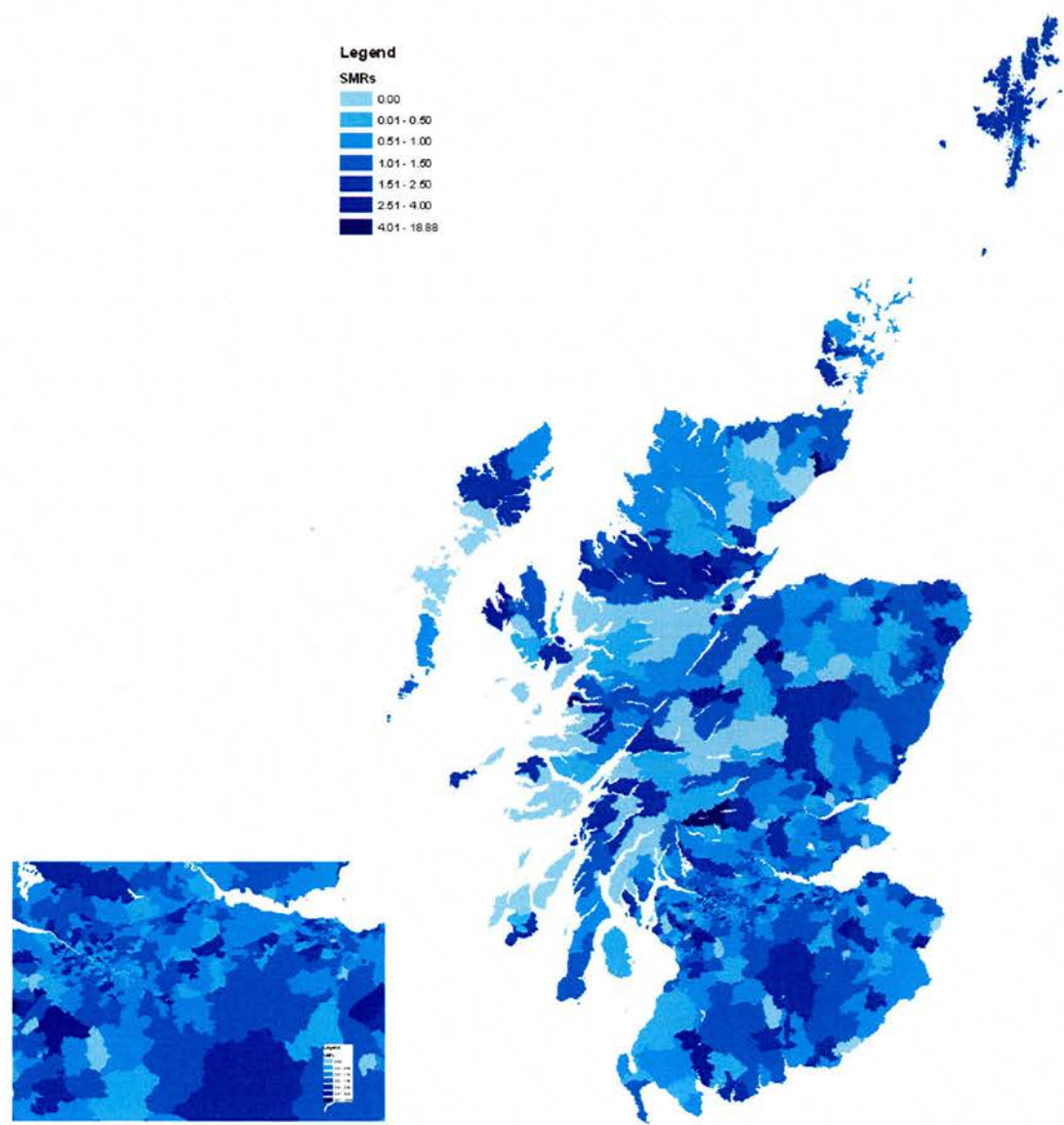


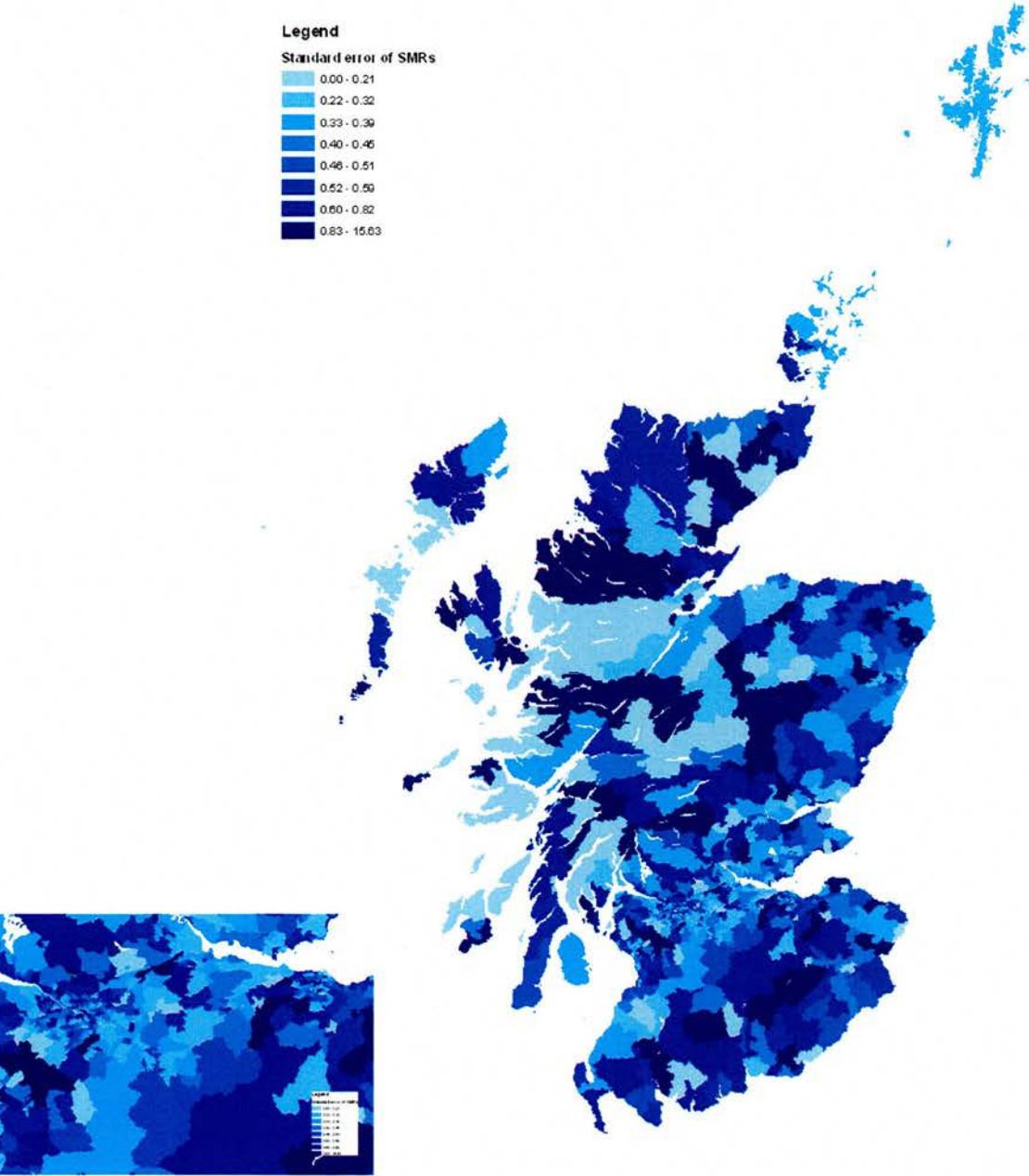
Figure 65 Testicular Cancer SMRs per 1991 postcode sectors: Scotland 1975-1999





The variability of the estimates of the SMRs can be assessed by standard error of each SMR. The distribution of the standard errors of the SMRs per postcode sector is skewed – range 0-15.6, median 0.45 and mean 0.58. The spatial variation of the standard errors is similar to the SMRs i.e. the SMRs may reflect the random variation of the estimates rather than any variation in disease risk (Figure 66). Therefore it is important to take into account this variability when calculating the Testicular Cancer disease risk, which can be done with Bayesian models.

**Figure 66** Testicular Cancer standard error of SMRs per 1991 postcode sector: Scotland 1975-1999



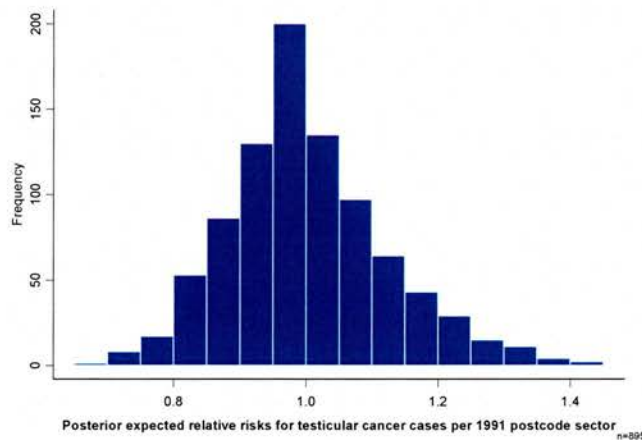
## 5.4 Bayesian Hierarchical Models of testicular cancer count data – Poisson-Gamma

The Poisson-Gamma model was run with the Testicular Cancer dataset in WinBUGs and converged following 20,000 iterations, a further 10,000 were run to produce robust posterior estimates.

### 5.4.1 Posterior estimates from model

The distribution of the Testicular Cancer posterior expected relative risks for each of the 1991 postcode sectors as produced by the Poisson-Gamma model is normally distributed unlike that for the SMRs (Figure 67).

**Figure 67** Histogram of Testicular Cancer posterior expected Relative Risk estimated from the Poisson-Gamma model



The range of values has been greatly reduced (0.67, 1.44) towards the population mean relative risk (1.004, standard deviation 0.02), whose variability has been reduced compared to the SMR (Table 28).

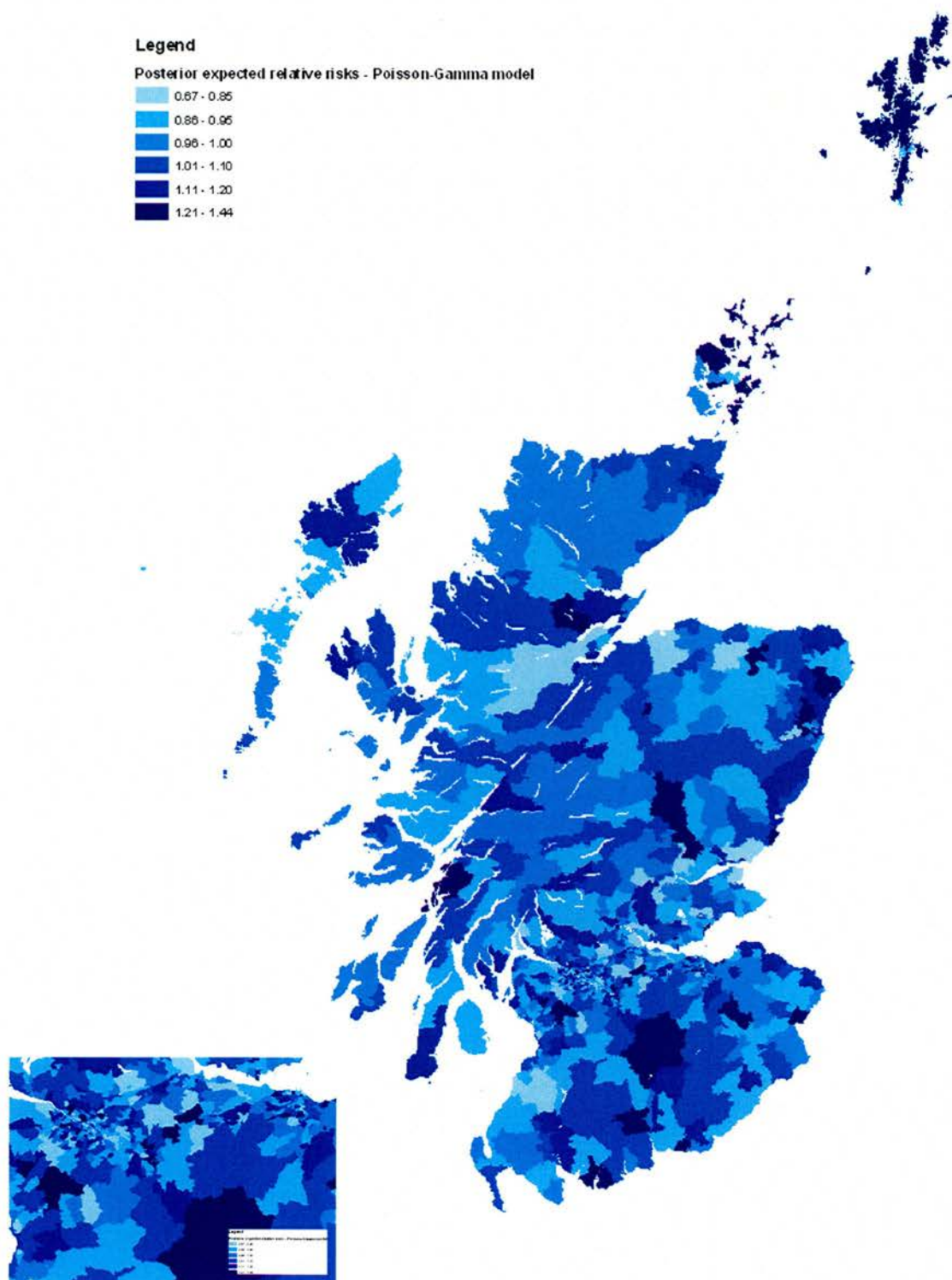
**Table 28** Posterior estimates for parameters in Poisson-Gamma model

Parameter	Mean	Standard Deviation	MC error	2.5% credible interval	Median	97.5% credible interval
a	12.53	1.701	0.1267	9.844	12.35	16.21
b	12.48	1.704	0.1266	9.785	12.29	16.18
mean	1.004	0.01987	4.13E-04	0.9658	1.004	1.044
var	0.08191	0.01097	7.86E-04	0.06174	0.08163	0.1033

So with the change in the variability of the estimate of the relative risks, has there been a change in their spatial variation? While the range of values of the relative

risks produced by the Poisson-Gamma model are greatly reduced compared to the SMRs there does not appear to be any spatial pattern to the estimates (Figure 68).

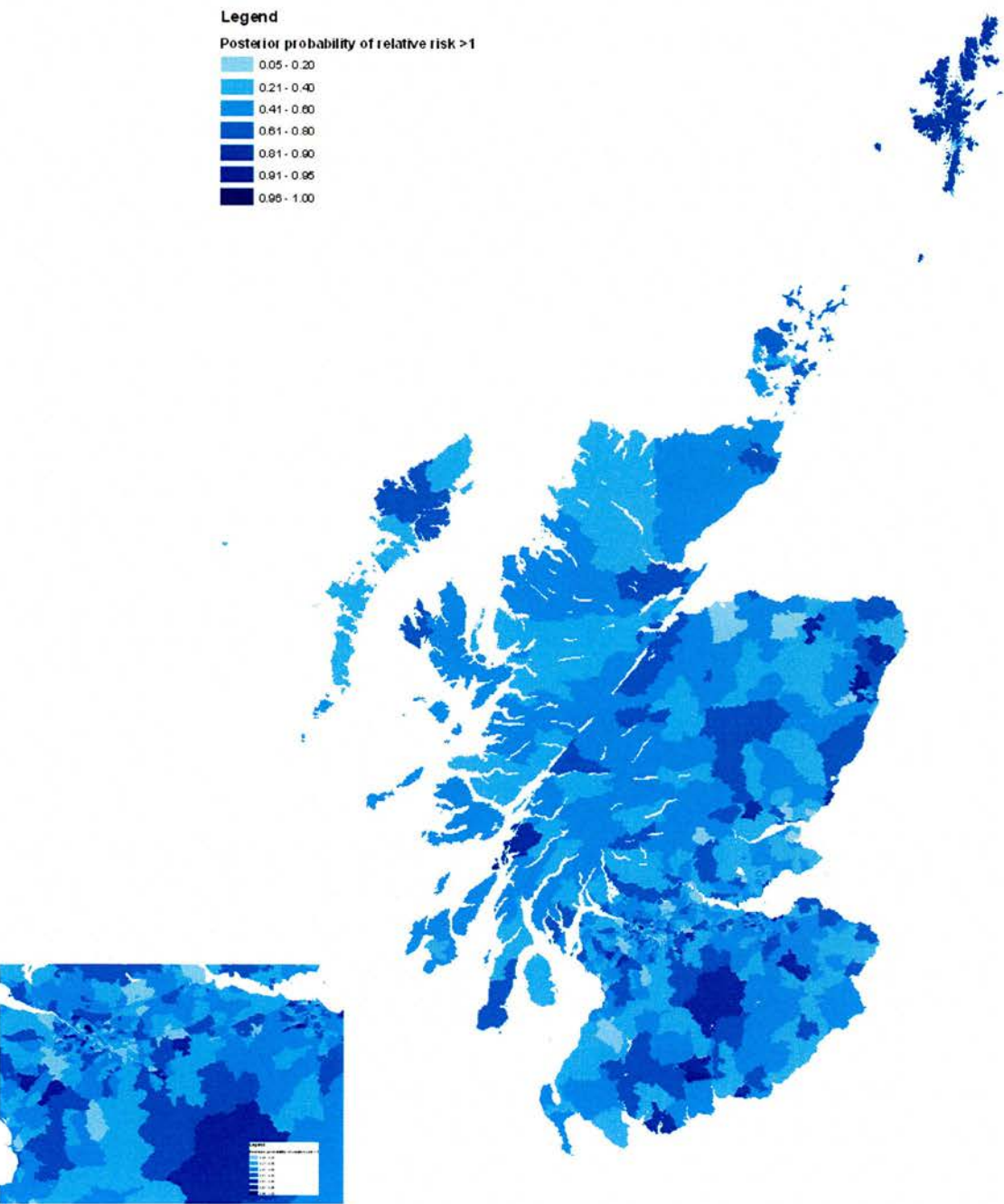
**Figure 68** Testicular Cancer posterior expected relative risk per 1991 postcode sector from the Poisson-Gamma model: Scotland 1975-1999





The probabilities of the relative risks being greater than 1 also show no spatial correlation, and that no areas of Scotland with probabilities greater than 0.95 (Figure 69). Therefore confirming there appears to be no spatial pattern to the relative risks produced by the Poisson-Gamma model, while taking into account the variability of the estimates.

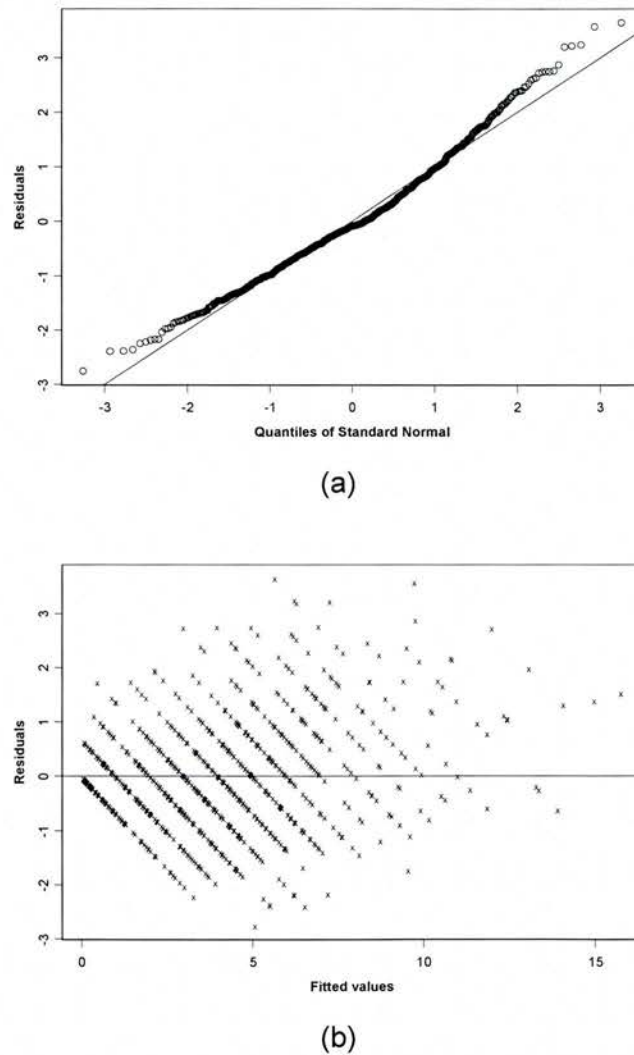
**Figure 69** Testicular Cancer posterior probability for expected relative risk greater than 1 per 1991 postcode sector from the Poisson-Gamma model: Scotland 1975-1999



### 5.4.2 Assessment of model

Although the relative risk estimates are smoothed by the Poisson-Gamma model, is the model successful at fitting the Testicular Cancer data? The analysis of the standardised residuals is shown in Figure 70.

**Figure 70** Poisson-Gamma Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted

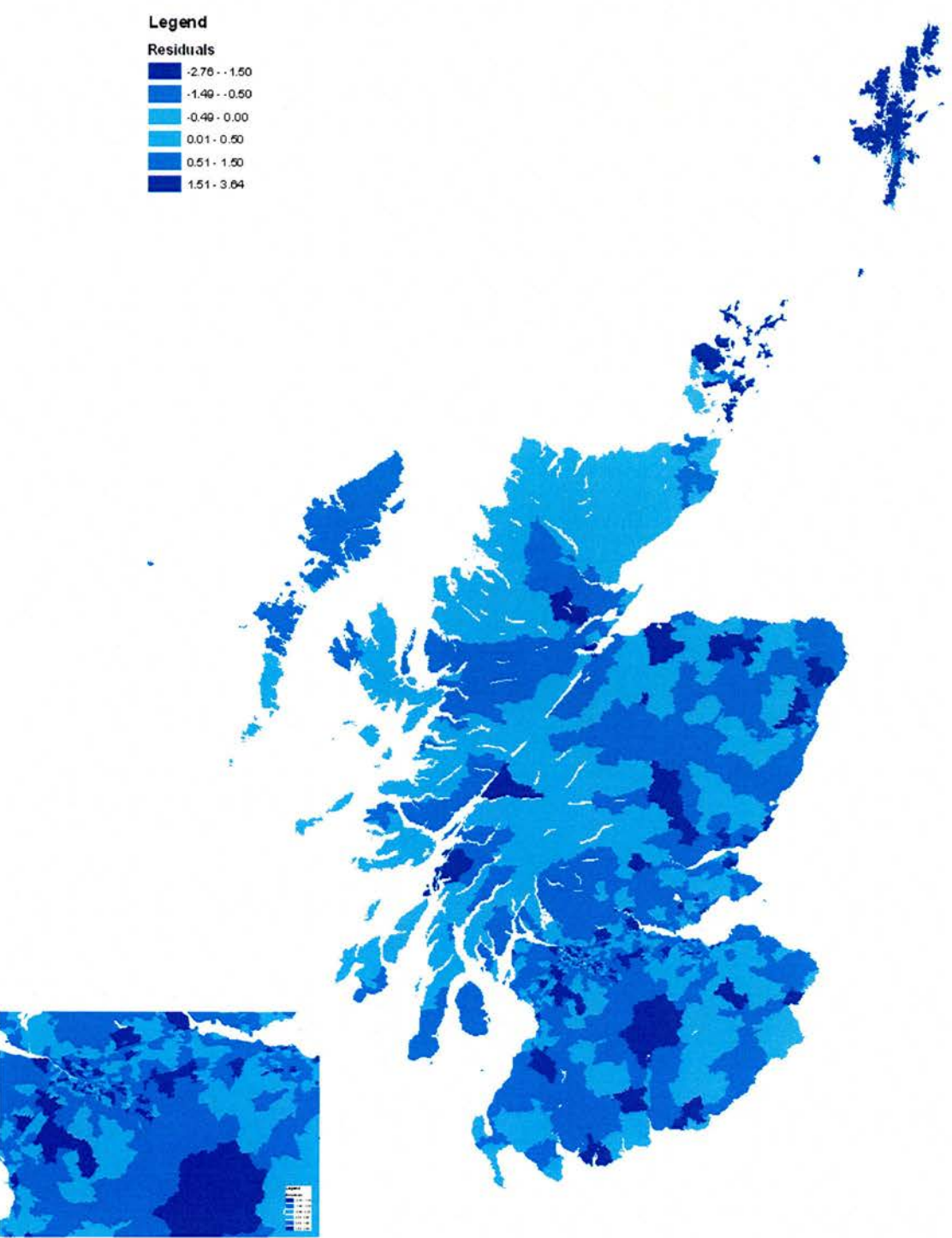


It would appear that the Poisson-Gamma model is only partly successful fit to the Testicular Cancer dataset. The normal plot (a) follows the x-y line, except for the extreme values of relative risks. Finally, the residuals are not evenly scattered across all fitted values (b), with more residuals above the  $y=0$  line which is increasingly the case with the larger fitted values. Therefore, while the Poisson-Gamma model

appears to smooth the relative risk estimates it does not appear to fit the testicular cancer dataset successfully, in particular for larger relative risks.

There might be a slight spatial correlation of the residuals, which would indicate that the unexplained variation is slightly spatially correlated (Figure 71).

**Figure 71** Testicular Cancer residuals of Poisson-Gamma model: Scotland 1975-1999





From the formal test there does not appear to be statistically significant ( $p=0.085$ ,  $r=0.035$ ) spatial correlation of the residuals (Table 29). So there is little indication that the heterogeneity of the relative risk estimates is spatially correlated.

**Table 29** Moran's I test result for residuals from Poisson-Gamma model

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.035 (-0.006, 0.076)
Correlation Normal p-value (2-sided)	0.085
Mean Permutation correlations (Inter-quartile range)	-0.0048 (-0.0235, 0.0108)
Permutation p-value	0.06

### 5.4.3 Conclusions for Poisson-Gamma model

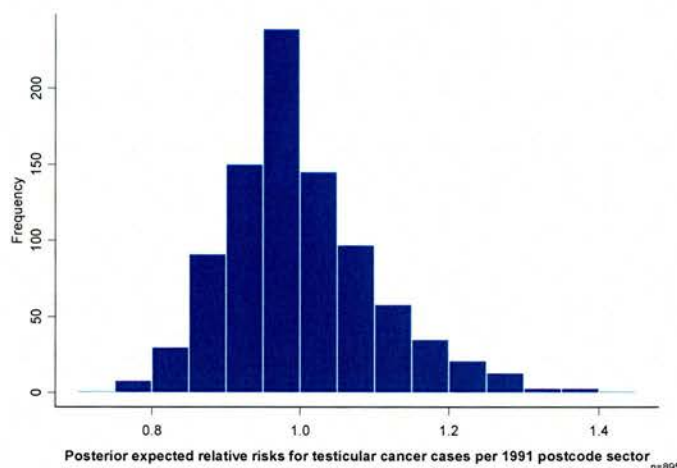
The relative risks estimated from the Poisson-Gamma model showed no spatial pattern, as with the SMRs. While the model smoothes the relative risks and so decreases the range of their values, it does not provide an adequate fit to the testicular cancer data. In particular those areas with high relative risks do not fit well within the model.

## 5.5 Bayesian Hierarchical Models of testicular cancer count data – Log-Normal

The Log-Normal model was run with the Testicular Cancer dataset in WinBUGs, convergence occurred following 3,000 iterations, and a further 10,000 were run to produce robust posterior estimates.

### 5.5.1 Posterior estimates from model

The distribution of the Testicular Cancer posterior expected relative risks for each of the 1991 postcode sectors as produced by the Log-Normal model is similar to those produced by the Poisson-Gamma model (Figure 72). The range of relative risks produced by the Log-Normal model (0.74, 1.41) is slightly narrower than those produced by the Poisson-Gamma (0.67, 1.44). Therefore, the Log-Normal model reduces the range of relative risks to a similar extent as the Poisson-Gamma model compared to the SMRs.

**Figure 72** Histogram of Testicular Cancer posterior expected Relative Risk estimated from the Log-Normal model

The Log-Normal smooths the relative risk estimates towards the overall mean relative risk, is 0.97 with a standard deviation of 0.02 (Table 30). So the population mean relative risk produced by the Log-Normal is lower than that produced by the Poisson-Gamma model (1.004) and the SMRs (1.02) and the variability of this estimate has been reduced compared to the SMR and reduced to the same extent as that done by the Poisson-Gamma model.

**Table 30** Posterior estimates for parameters in Log-Normal model

Parameter	Mean	Standard Deviation	MC error	2.5%	Median	97.5%
alpha	-0.03119	0.01972	2.92E-04	-0.07034	-0.03108	0.007648
mean	0.9695	0.01911	2.83E-04	0.9321	0.9694	1.008
tau.v	16.02	2.524	0.1024	11.66	15.82	21.57

The spatial variation of the relative risk estimates produced by the Log-Normal model is very similar to that produced by the Poisson-Gamma model (Figure 73), i.e. there does not appear to spatial correlation of the relative risks.

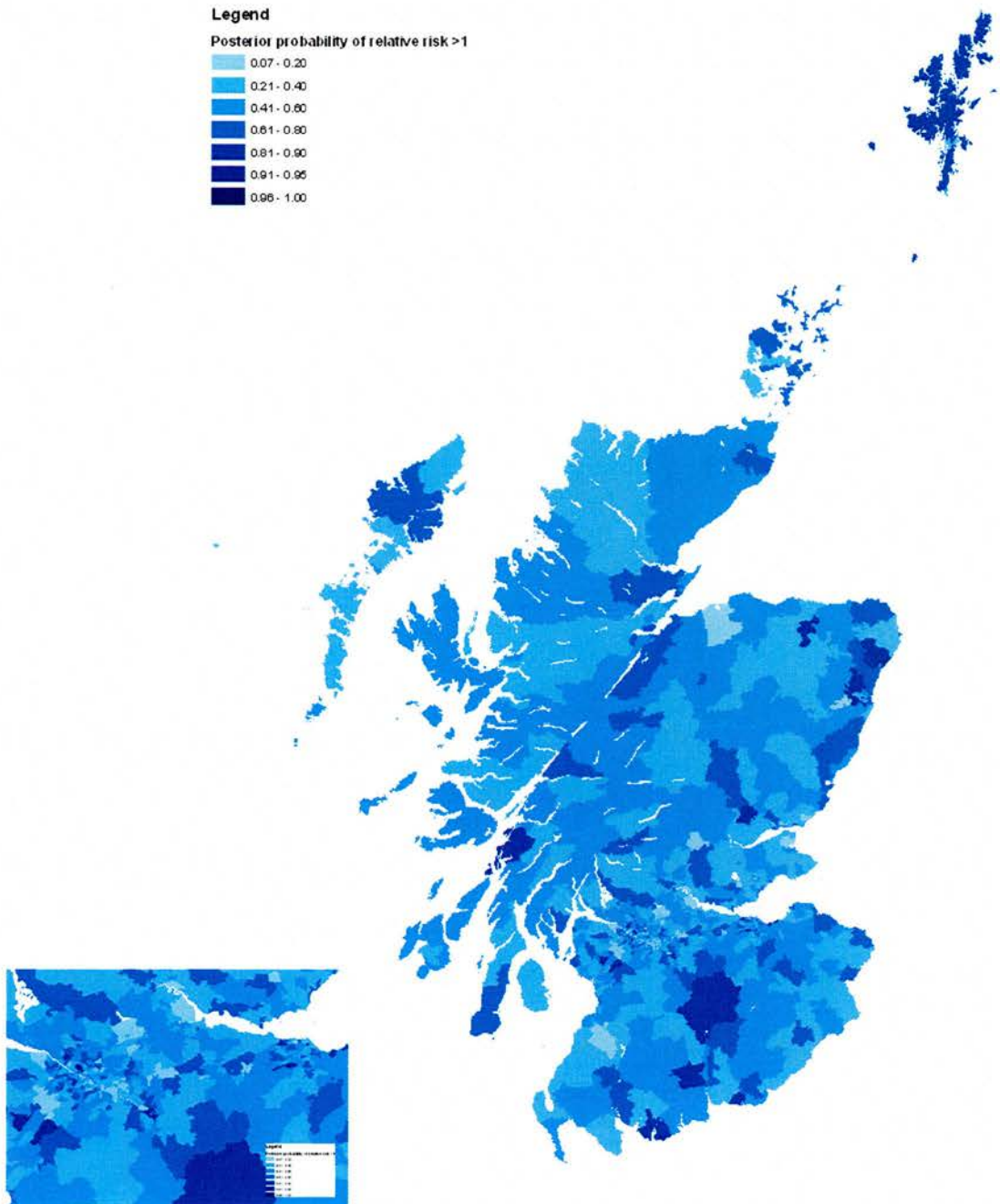
**Figure 73** Testicular Cancer posterior expected relative risk per 1991 postcode sector from the Log-Normal model: Scotland 1975-1999





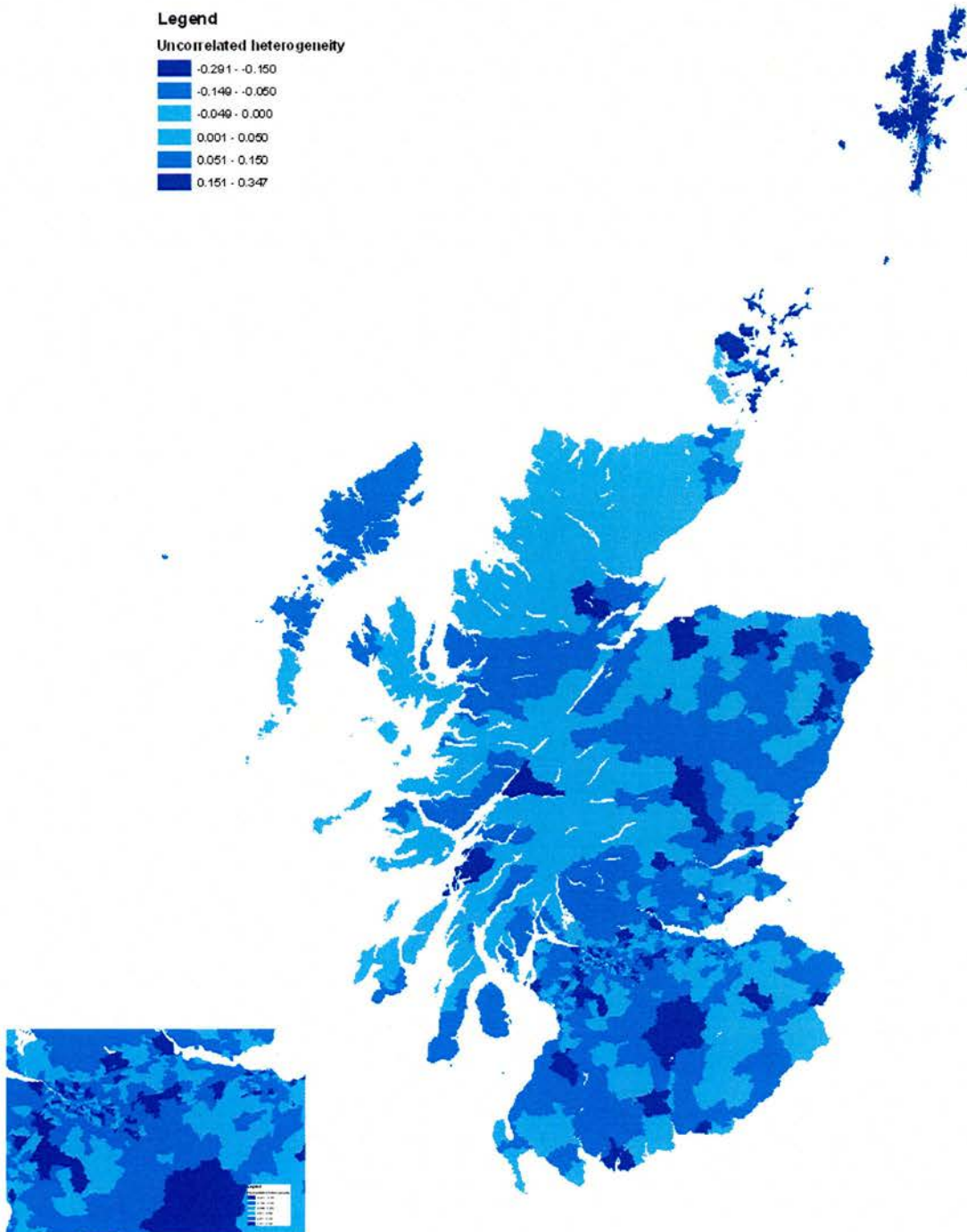
The probabilities of the relative risks being greater than 1 show a similar pattern to the relative risks with no areas of Scotland with probabilities greater than 0.95 (Figure 74). Therefore some evidence that there is no spatial pattern to the relative risks produced by the Log-Normal model, as with the Poisson-Gamma model, while taking into account the variability of the estimates.

**Figure 74** Testicular Cancer posterior probability of relative risk being greater than 1 per 1991 postcode sector from the Log-Normal model: Scotland 1975-1999



The map of the uncorrelated heterogeneity term of this term will show if there is a spatial clustering of the extra variation of the relative risks estimates (Figure 75). It does not appear to be any spatial correlation of the heterogeneity terms, so it does not appear to vary in a spatially structured way.

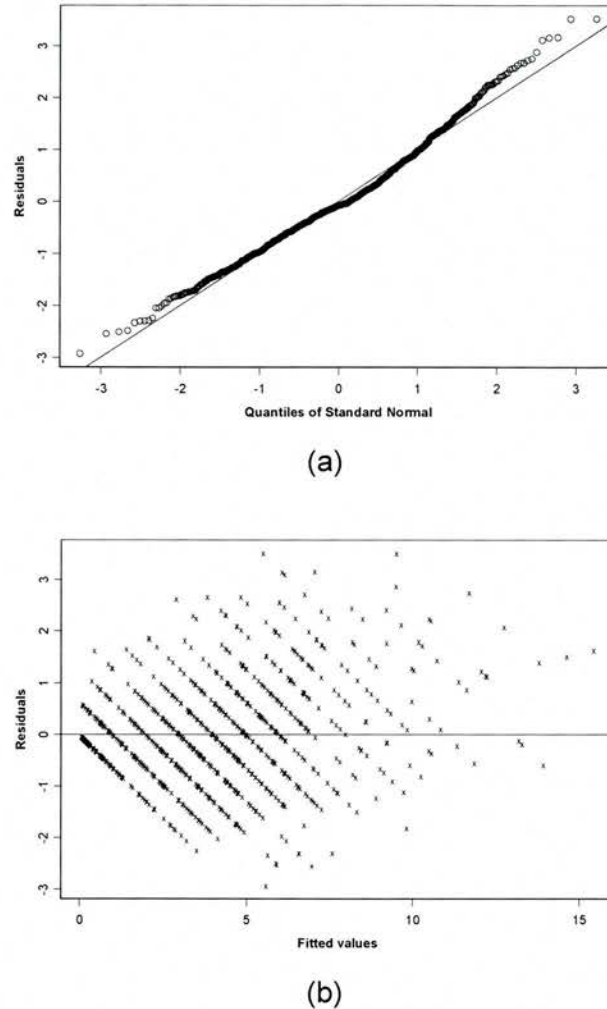
**Figure 75** Testicular Cancer posterior probability of uncorrelated heterogeneity per 1991 postcode sector from the Log-Normal model: Scotland 1975-1999



### 5.5.2 Assessment of model

The analysis of the standardised residuals produced for each relative risk estimate from the Log-Normal model is shown in Figure 76.

**Figure 76 Log-normal Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted**

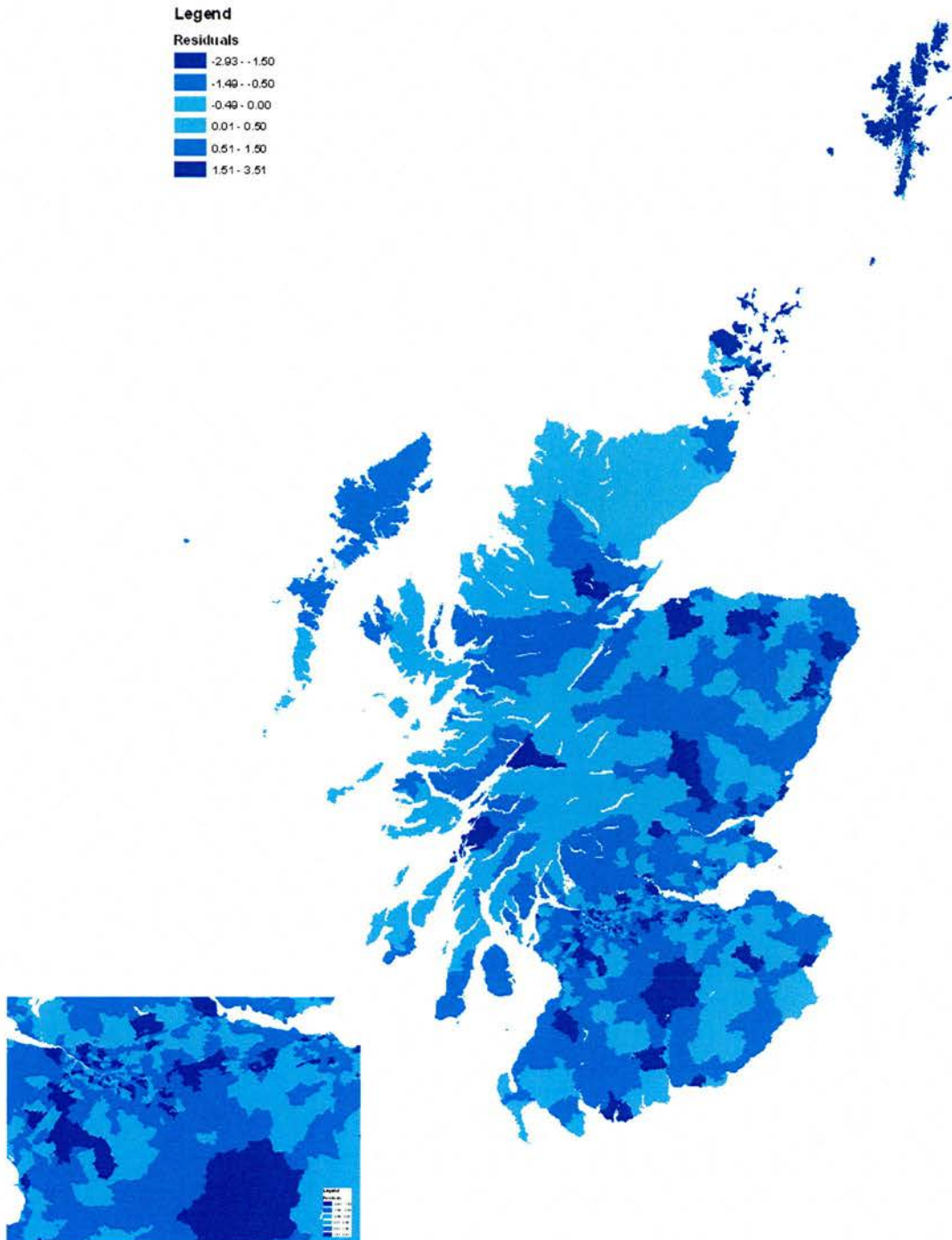


It would appear that the Log-Normal fits the Testicular Cancer slightly better than the Poisson-Gamma model; however it is not adequate. The normal plot (a) shows that most of the residuals follow the x-y line, except again for the extreme values although they are nearer the line than the Poisson-Gamma results. As with the Poisson-Gamma model the residuals are not evenly scattered across all fitted values (b), with more residuals above the  $y=0$  line which is increasingly the case with the larger fitted values.



The spatial variation of the residuals produced by the Log-Normal model is similar to those produced by the Poisson-Gamma model i.e. there appears to be no spatial correlation (Figure 77). So it would appear that the Log-Normal model, like the Poisson-Gamma model, there dos appear to be a spatial component to the heterogeneity of the relative risks.

**Figure 77 Testicular Cancer residuals of Log-Normal model: Scotland 1975-1999**



From the formal test there does not appear to be statistically significant ( $p=0.094$ ,  $r=0.034$ ) spatial correlation of the residuals Table 31. There is no evidence of a spatial correlation of the residuals, so the heterogeneity does not appear to vary in a spatially structured way.

**Table 31** Moran's I test result for residuals from Log-Normal model

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.034 (-0.007, 0.0750)
Correlation Normal p-value (2-sided)	0.094
Mean Permutation correlations (Inter-quartile range)	0.0007 (-0.0133, 0.0132)
Permutation p-value	0.05

### 5.5.3 Conclusions for Log-Normal model

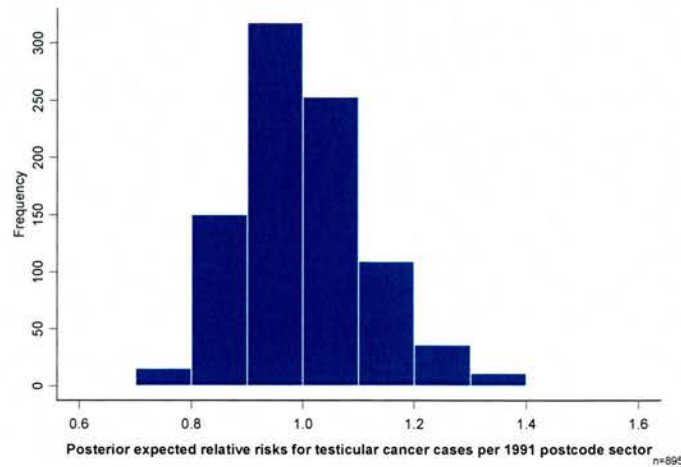
The Log-Normal model only seems to be a slight improvement on the Poisson-Gamma model for estimating the relative risks for the Testicular Cancer dataset. Both show no spatial variation of the relative risk of testicular cancer. However, the residual analysis of the Log-Normal model shows that is a better fit to the Testicular Cancer dataset than the Poisson-Gamma model, although it is not completely adequate. From assessing the spatial variation of the residuals the heterogeneity of the relative risk estimates does not vary in a spatially correlated way.

## 5.6 Bayesian Hierarchical Models of testicular cancer count data - Besag, York and Mollié (BYM) model

The BYM model was run with the Testicular Cancer dataset in WinBUGs which converged following 8,000 iterations and a further 10,000 were run to produce robust posterior estimates.

### 5.6.1 Posterior estimates from model

Figure 78 shows the distribution of the posterior expected relative risks estimated from the BYM model. The distribution of the estimates is very similar in shape to both the Poisson-Gamma and Log-Normal models. The maximum relative risk (1.55) is the largest produced by any of the three Bayesian models, while the minimum value (0.68) is between the other two models.

**Figure 78** Histogram of Testicular Cancer posterior expected Relative Risk estimated from the BYM model

The population mean relative risk is 0.97 is similar to that produced in the Log-Normal model and slightly lower than the SMR and that produced by the Poisson-Gamma model (Table 32). The intercept term  $\alpha$  has decreased and the precision of the non-spatial heterogeneity term has deteriorated, compared to the Log-Normal model. Therefore the inclusion of the spatially correlated heterogeneity term has weakened the intercept term and the precision of the non-spatial heterogeneity.

**Table 32** Posterior estimates for non postcode specific parameters in BYM model

Parameter	Mean	Standard Deviation	MC error	2.5%	Median	97.5%
$\alpha$	-0.02895	0.02188	0.001037	-0.07281	-0.0286	0.01329
mean	0.9717	0.02124	0.001005	0.9298	0.9718	1.013
$\tau_{u,u}$	12	2.328	0.1224	7.837	11.8	17.16
$\tau_{u,v}$	988.7	983.3	92.66	112.8	625.2	3773

The map of the posterior expected relative risks produced by the BYM model shows a very different spatial pattern than the Poisson-Gamma and Log-Normal models (Figure 79). The inclusion of the spatially correlated heterogeneity term within the model has meant that the relative risk have a spatial correlation – low relative risks in the central belt area with higher risk areas in the other areas, almost a rural/urban difference.

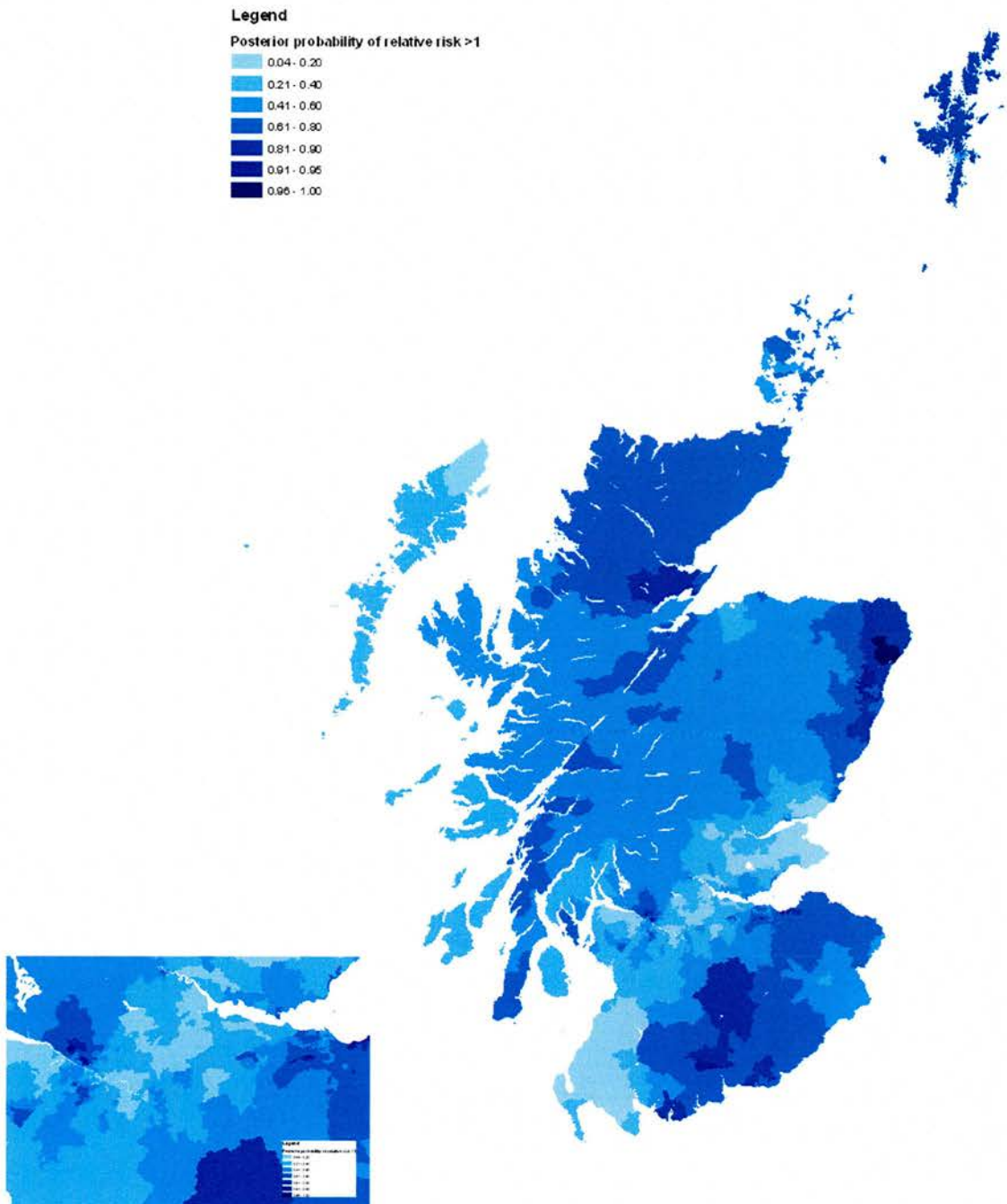


**Figure 79** Testicular Cancer posterior expected relative risk per 1991 postcode sector from the BYM model: Scotland 1975-1999



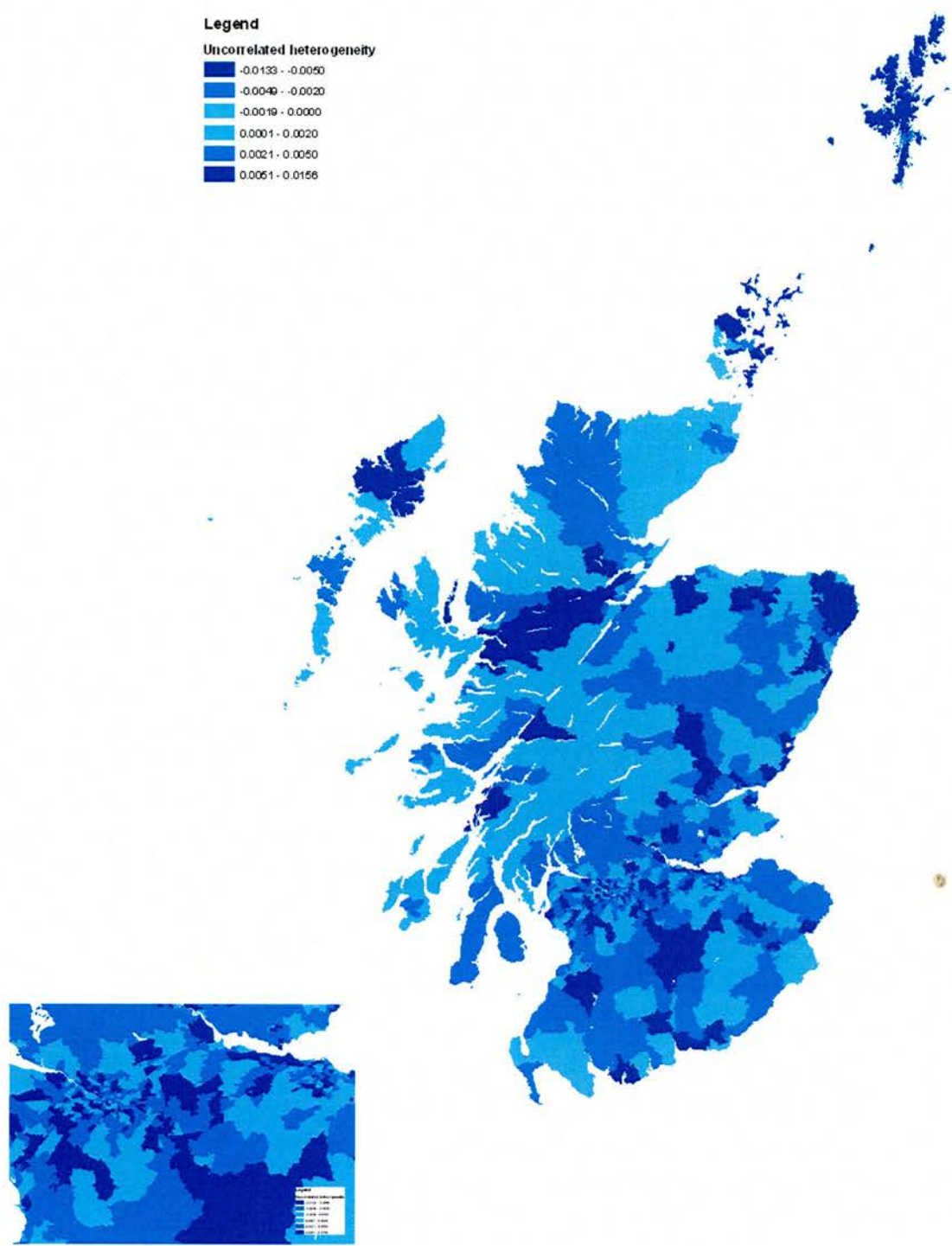
This spatial pattern of the relative risks is repeated in the probabilities of the relative risks being greater than 1 (Figure 80). However those areas with the highest relative risks do not all have probabilities greater than 0.95. Therefore the probabilities do not confirm the spatial variation of the relative risks produced by the BYM model while taking into account the variability of the estimates.

**Figure 80** Testicular Cancer posterior probability for expected relative risk greater than 1 per 1991 postcode sector from the BYM model: Scotland 1975-1999



As with the Log-Normal model, the non spatial heterogeneity does not appear to have any spatial correlation (Figure 81).

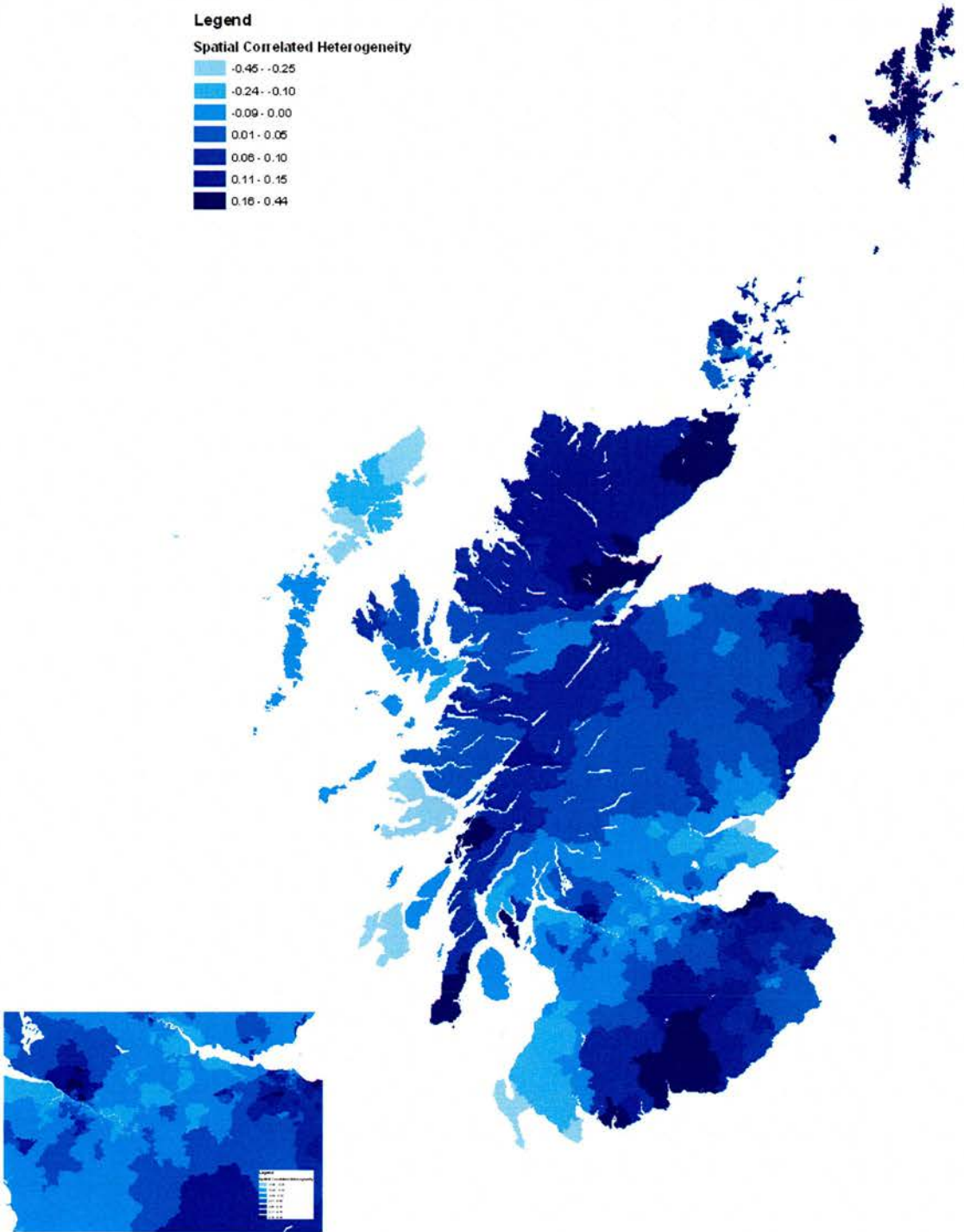
**Figure 81** Testicular Cancer posterior expected uncorrelated Heterogeneity term  $v_i$  per 1991 postcode sector from the BYM model: Scotland 1975-1999





The spatially correlated heterogeneity term does show spatial correlation similar to that of the relative risks (Figure 82). Therefore from the BYM model the variability of the random effects might have a spatial component.

**Figure 82** Testicular Cancer posterior expected correlated Heterogeneity term  $u_i$  per 1991 postcode sector from the BYM model: Scotland 1975-1999



The spatial variation shown in this map could be because there is a spatially correlated variability to the estimates of the relative risks, which is now accounted for by this term within the BYM model. However, it could be that the CAR model used in the BYM model for the spatially correlated heterogeneity term over-smoothes the relative risks. This might explain the deterioration in the precision value for the non-spatially correlated heterogeneity term between the Log-Normal and BYM model. Furthermore, in the previous models, no spatial correlation of the relative risk estimates, the heterogeneity or the residuals was found.

### 5.6.2 Sensitivity Analysis

Table 33 shows the results of the comparison of the relative risks estimated by the BYM model outlined (Model 1) and those from the BYM model where the prior for  $\tau.u$  is changed to  $\text{gamma}(0.5, 0.0005)$ . There appears to be a strong correlation between the two sets of estimated relative risks, and no significant differences in the relative risks estimated for the same postcode sector. Therefore the distinct spatial pattern of the relative risks estimated by the BYM are not due to specific prior for the precision of the spatially correlated heterogeneity.

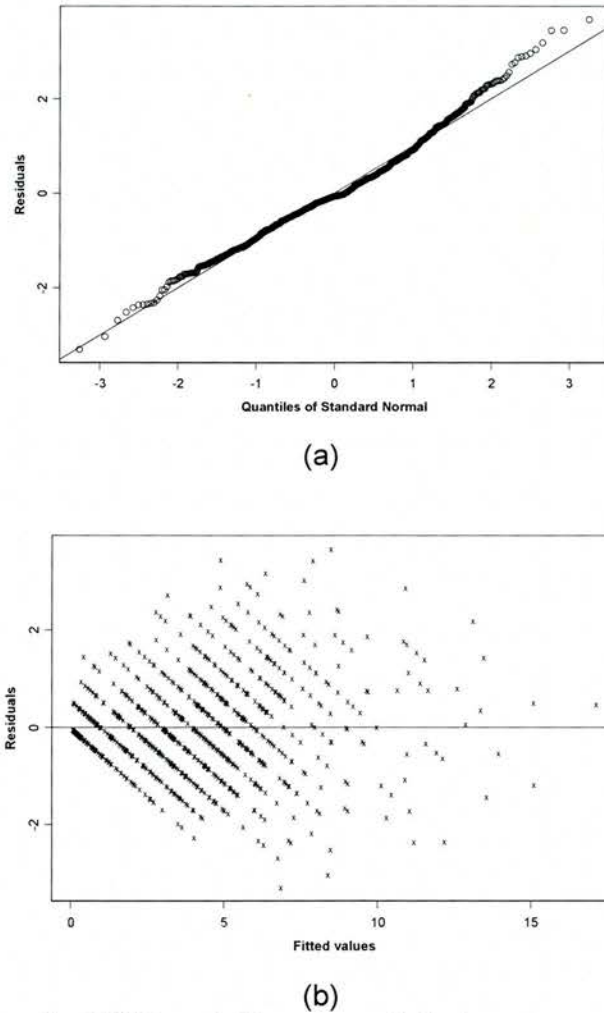
**Table 33 Comparison tests of Relative Risks estimated from BYM models using prior for  $\tau.u$   $\text{gamma}(1,1)$  (model 1) and  $\text{gamma}(0.5, 0.0005)$  (model 2)**

Correlation co-efficient of relative risks	Mean difference in relative risks (95% CI) (Model 1-2)	Paired t-test – p value
0.996	0.00014 (-0.0005, 0.0008)	0.6756

### 5.6.3 Assessment of model

The residual analysis for the BYM model is shown in Figure 83.

**Figure 83** BYM Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted



It would appear that the BYM model is a very slight improvement than the other two Bayesian model from the residual analysis. For the Normal Plot of the residuals (a) most of the residuals follow the x-y line, except again for the extreme values although they are nearer the line than the other models results. For the residuals plotted by the fitted values, (c), there is slight improvement.

There does appear to be a little spatial correlation of the residuals (Figure 84). The apparent correlation of low residuals is seen in the North-West of Scotland, where the relative risks are high.



Figure 84 Testicular Cancer residuals of BYM model: Scotland 1975-1999



According to the Moran's I test there is a statistically significant ( $p=0.001$ ) although small spatial correlation ( $r=-0.069$ ) of the residuals (Table 34). Therefore the unexplained variation is spatially correlated.

**Table 34** Moran's I test result for residuals from BYM model

Statistic	Result
Number of permutations	100
Correlation (95% CI)	-0.069 (-0.110, -0.028)
Correlation Normal p-value (2-sided)	0.001
Mean Permutation correlations (Inter-quartile range)	-0.0023 (-0.0147, 0.0140)
Permutation p-value	1

It is possible to compare the DIC diagnostics of the three Bayesian Hierarchical models to assess which is the best fit to the testicular cancer data (Table 35). These results mirror the conclusions found from the residual analysis, i.e. the BYM model fits the Testicular Cancer datasets the best and the Poisson-Gamma model is the least successful.

**Table 35** Model fitting results of the three disease count models

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
Poisson-Gamma model	3263.34	3066.11	197.23	3460.57
Log-Normal model	3285.66	3116.47	169.184	3454.84
BYM model	3342.79	3237	105.787	3448.57

#### 5.6.4 Conclusions for BYM model

The BYM model is slightly better model and fit to the data compared to the Poisson-Gamma or Log-Normal model, when comparing the residuals analysis and the DIC results. However, it like the other two models is not fully successful in accounting for the unexplained variation in the relative risks. While the other two models did not find spatial correlation of the relative risk estimates, the heterogeneity or the residuals, they were found in the BYM model. The spatial correlation of the unexplained variation lends credence to the possibility that the spatially correlated heterogeneity term over-smoothes the spatial correlation.

### 5.7 Inclusion of covariates into Bayesian hierarchical models of disease count data

The inability of any of the three Bayesian Hierarchical Models to fully account for the spatial variation of the testicular cancer risks might not be just due to the terms used within the models, but that other explanatory variables might explain the variation. This section assesses if the inclusion of potential explanatory variables explains the variation of relative risks.

#### 5.7.1 Comparison of models

Table 36 shows the different models run in WinBUGs and the results for each of the DIC diagnostics. These results are the primary analysis used to assess which model is the most successful at fitting the Testicular Cancer dataset.

**Table 36    Model fitting results of the Bayesian Hierarchical disease count models with covariates**

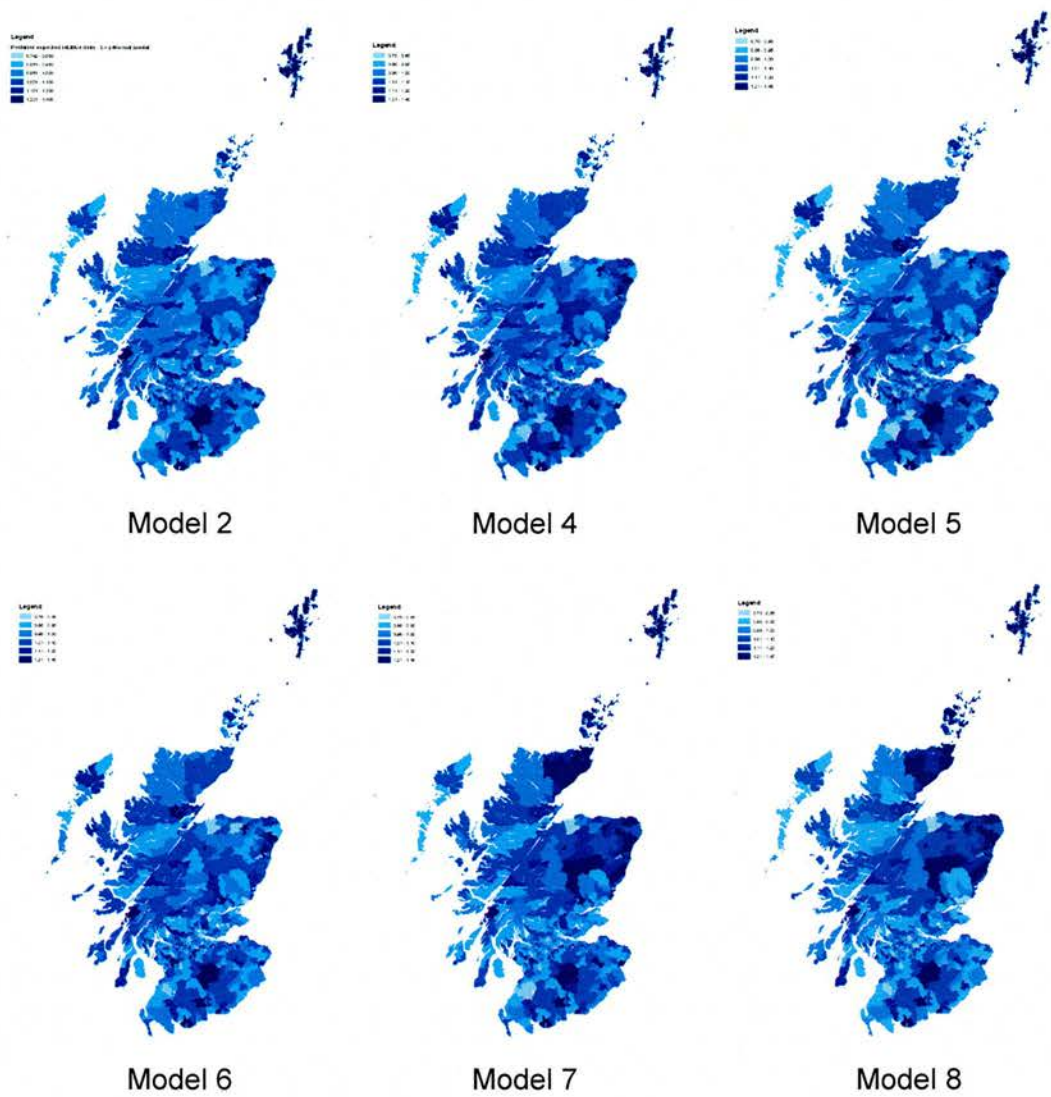
Model	$\overline{D}$	$D(\overline{\vartheta})$	pD	DIC
1. Poisson-Gamma model	3263.34	3066.11	197.23	3460.57
2. Log-Normal model	3285.66	3116.47	169.184	3454.84
3. BYM model	3342.79	3237	105.787	3448.57
4. Log-Normal model plus deprivation (5 groups)	3284.74	3113.89	170.844	3455.58
5. Log-Normal model plus deprivation (7 groups)	3284.51	3113.67	170.837	3455.35
6. Log-Normal model plus urban/rural indicator	3280.81	3115.38	165.436	3446.25
7. Log-Normal model plus radon (mean)	3283.04	3117.88	165.158	3448.2
8. Log-Normal model plus radon (% >200)	3287.77	3116.36	171.41	3459.18
9. BYM model plus deprivation (5 groups)	3260.85	3043	217.852	3478.71
10. BYM model plus deprivation (7 groups)	3260.17	3041.23	218.937	3479.11
11. BYM model plus urban/rural indicator	3347.56	3241.59	105.976	3453.54
12. BYM model plus radon (mean)	3286.18	3115.46	170.717	3456.89
13. BYM model plus radon (% >200)	3263.25	3050.35	212.892	3476.14



The inclusion of the mean radon levels or the rural/urban indicator explain some of the spatial variation in the Testicular Cancer risk in the Log-Normal model. However, when the spatially correlated heterogeneity is added to the models, as is the case in the BYM model, no model with the inclusion of potential covariates are an improvement on the BYM model. This conclusion is made from comparing DIC results; however, it would appear that the deviances are improved in the BYM model when all the covariates, except the rural/urban indicator, are included. Therefore the data fits the Testicular Cancer risk better with the inclusion of most of the covariates, but they are not better models when the number of parameters is taken into account. Could this be because the extra variation is soaked up by the spatially heterogeneity term and so could not be accounted for by the potential covariates? A comparison of the posterior estimates produced by these models might indicate what terms are accounting for the spatial variation in the Testicular Cancer risk.

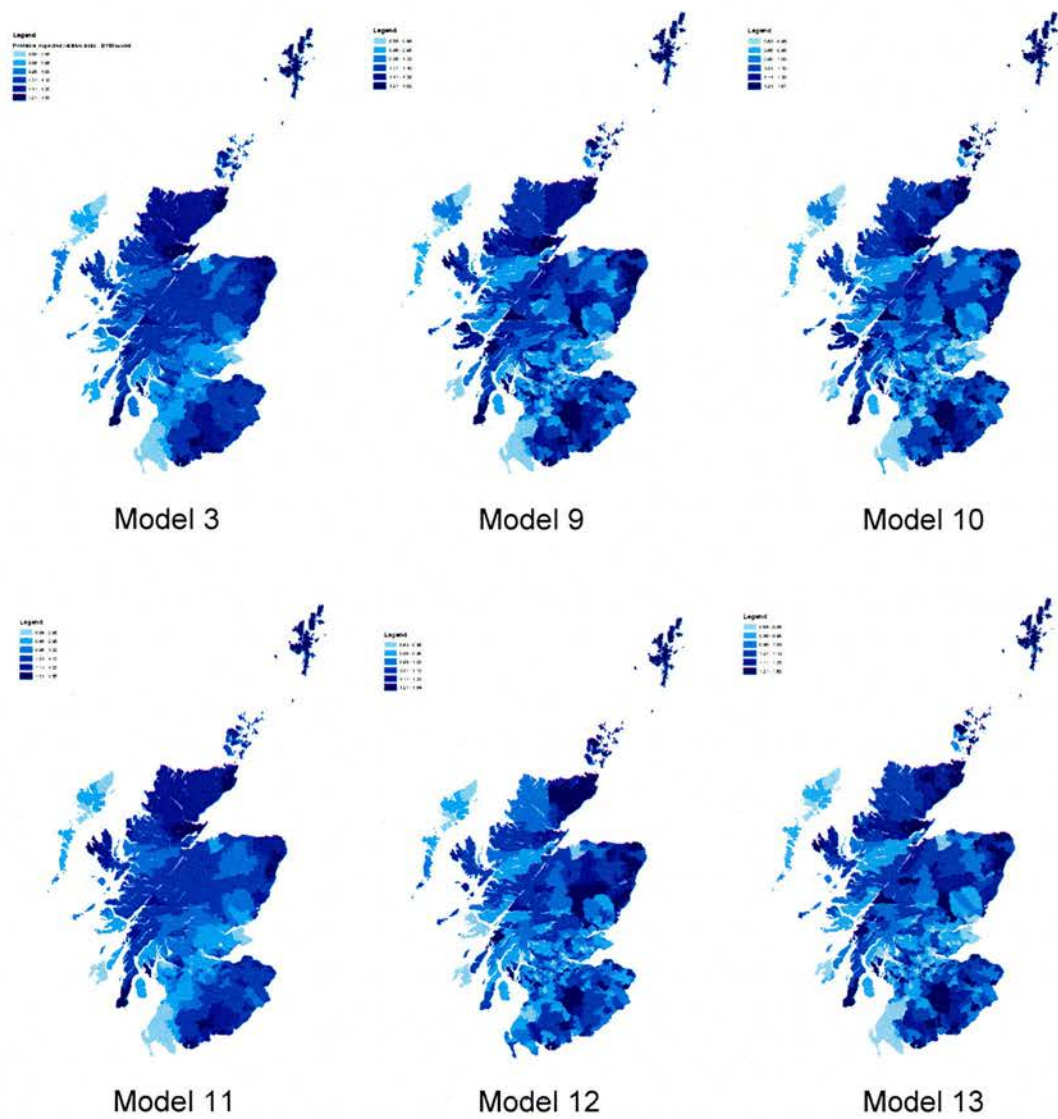
Figure 85 shows the relative risks produced by the six Log-Normal models described in Table 36. In order to compare the spatial variation of the different models the same categories are used in the maps and it would appear that most show the same spatial pattern as the Log-Normal model i.e. no spatial correlation. However, the spatial pattern of the relative risks the Log-Normal plus the two radon measurements (models 7 and 8) appear slightly different. There does appear to be some clustering of high relative risks in the North-East of Scotland. The mean radon model (7) is an improvement on the Log-Normal model when comparing DIC results, so there might be an association between the relative risk and mean radon.

**Figure 85** Testicular cancer posterior expected relative risk from Log-normal plus variable models



Would the inclusion of the spatially correlated heterogeneity term to these models alter the spatial pattern of the relative risks? Figure 86 shows the relative risks produced by the six BYM models described in Table 36. The inclusion of covariates in the BYM model has reduced the spatial correlation of the relative risks, except with the urban/rural indicator (Model 11). This model has a similar spatial variation of relative risk to the model without covariates and is in fact the best model of those with covariates when comparing DIC results.

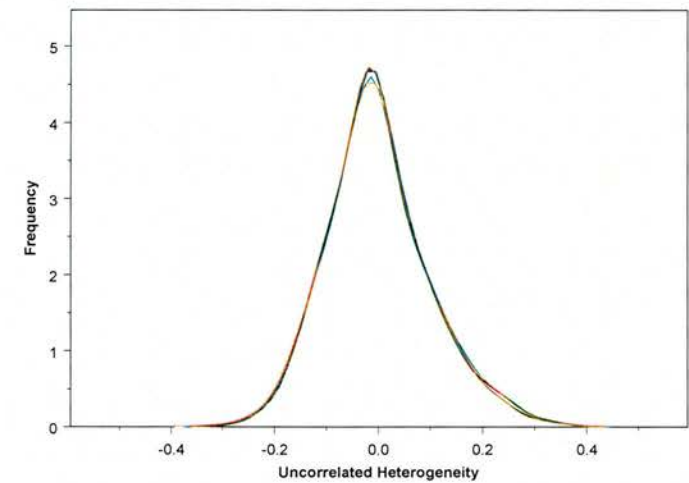
**Figure 86** Testicular cancer posterior expected relative risk from BYM plus variable models



The difference the heterogeneity terms produced in the models might show what variation is accounted for by the inclusion of potential covariates. The distribution of the non-spatially correlated heterogeneity term is unaffected by the inclusion of covariates within the Log- Normal model (Figure 87). So the random heterogeneity produced by the Log-Normal model is not altered, even with the inclusion of possible covariates. Therefore none of the possible covariates appear to account for any of the random extra variation within the Log-Normal model.

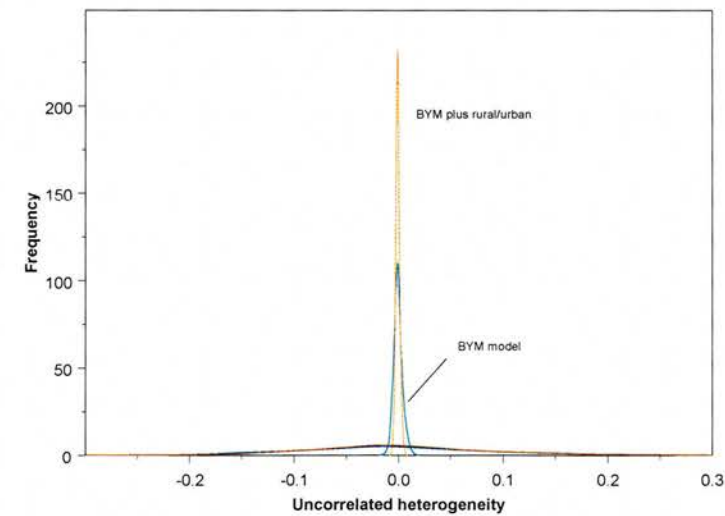


**Figure 87** Testicular cancer posterior spatially uncorrelated heterogeneity term from Log-normal plus variable models



The same conclusion can be made when comparing the distributions of the non-spatially correlated heterogeneity term produced by the BYM models, except for the urban/rural indicator model (Figure 88).

**Figure 88** Testicular cancer posterior spatially uncorrelated heterogeneity term from BYM plus variable models

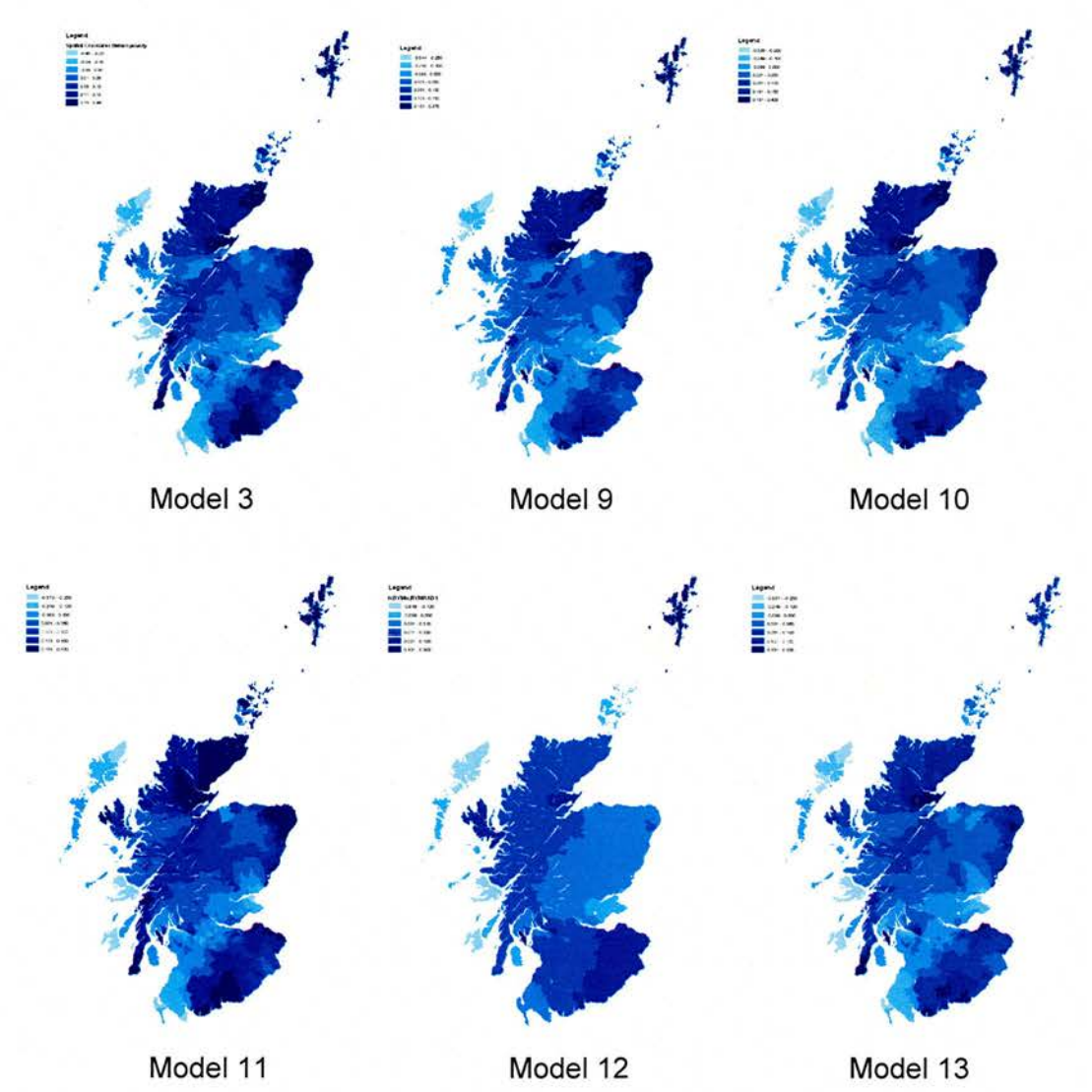


The BYM model without a covariate included and the BYM model with the urban/rural indicator have a smaller range of values than the other models. Furthermore, the model with the rural/urban indicator has a narrower distribution compared to the BYM without a covariate model. Therefore, the rural/urban

indicator appears to account for some of the random extra variation within the BYM model.

The spatial variations of the spatially correlated heterogeneity term produced by the BYM models have similar patterns, except the model including mean radon (Figure 89). This model (Model 12) shows much less variation of values for the spatially correlated heterogeneity term than the other models. Therefore it would appear that the mean radon accounts for some of the spatially correlated extra variation within the BYM model.

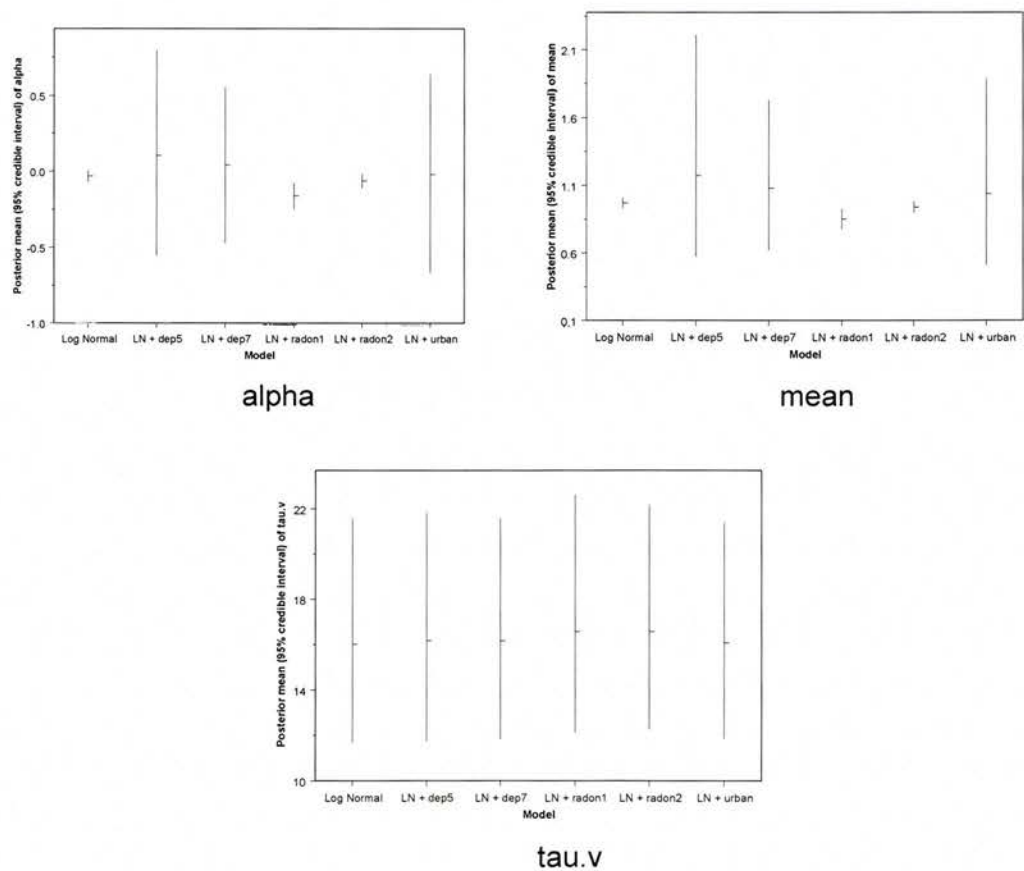
**Figure 89** Testicular cancer posterior spatially correlated heterogeneity term from BYM plus variable models



The comparison of the posterior estimates and the DIC results indicate that the relative risks of testicular cancer are associated with the urban/rural indicator and mean radon. The DIC results from the Log-Normal models appear to indicate that the model is improved with the inclusion of these covariates. However, the DIC results of the BYM mode did not confirm this. The changes in the spatial variation of the heterogeneity terms for these models could mean that they have explained some of the extra variation; but the CAR model used as the spatial heterogeneity term over-smoothes the extra variation which we wish to account for.

Apart from the postcode specific posterior estimates produced by the models, there are model parameters that might provide more information on how successful the inclusion of potential covariates have been in explaining the spatial variation of the testicular cancer risk. Figure 90 shows the posterior estimates of the parameters for the different Log-Normal models.

**Figure 90** Posterior estimates for non postcode specific parameters in Log-Normal models





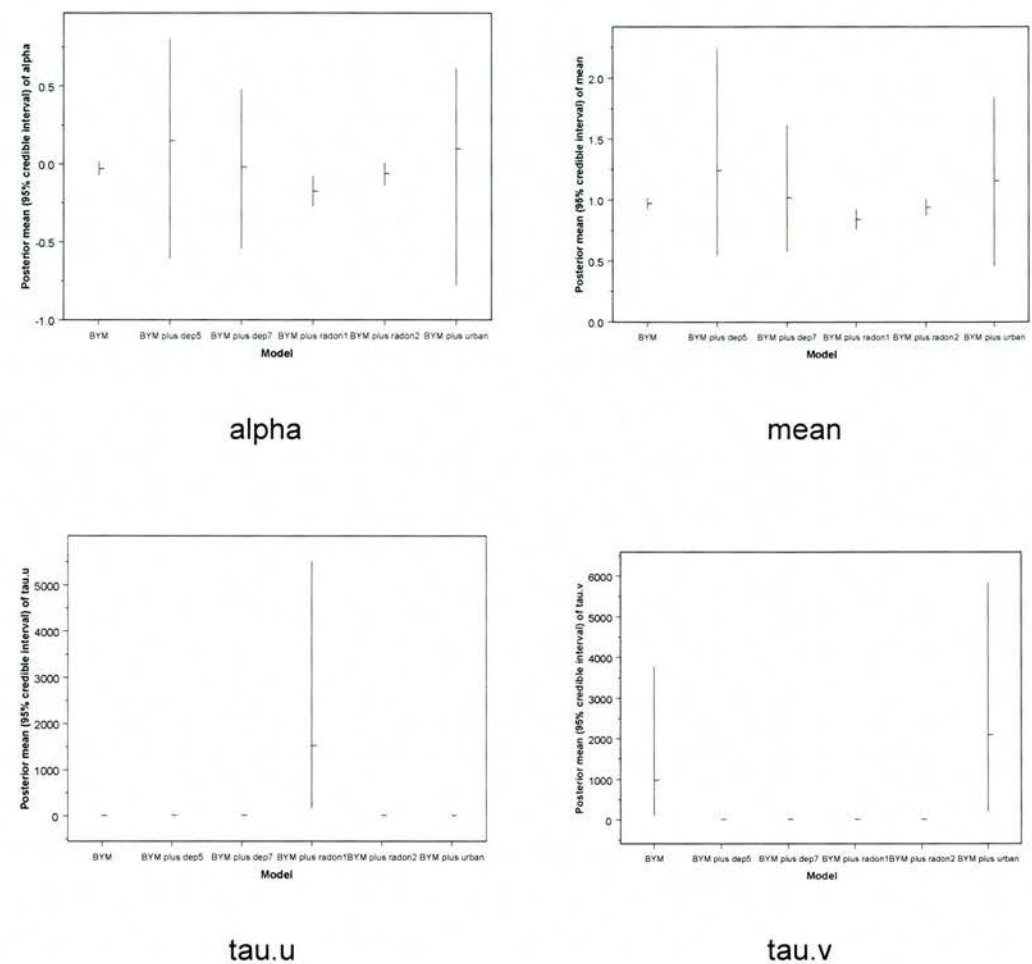
The inclusion of both radon measurements has resulted in the mean intercept term becoming more negative compared to the basic Log-Normal model. These terms had also changed the spatial variation of the relative risks. The models with the other covariates have not altered their estimates of the mean intercept term although their credible intervals have widened. Therefore for those models with covariates that have changed the spatial variation of the relative risk the strength of the intercept term has increased. However, those models that did not change the spatial variation of the relative risk have not changed the intercept term but diminished the precision of its estimate.

The population mean relative risk (mean) estimates show as similar pattern to the intercept estimate. Therefore the models with covariates (i.e. radon measurements) that have changed the spatial variation of the relative risks have reduced the overall population relative risk. Furthermore, those models that did not alter the spatial variation of the relative risk estimates have increased the population relative risk, although the precision of these estimates are such that it is inconclusive that there are changes.

Finally, the precision of the non-spatially correlated heterogeneity term ( $\tau.v$ ) is unaltered by inclusion of the possible covariates.

Do any of these parameter estimates alter with the inclusion of the spatially correlated heterogeneity term? The intercept term and the population relative risk estimates are largely unaltered by the inclusion of the spatially correlated heterogeneity term (Figure 91). However the precision of the non-spatially correlated heterogeneity term ( $\tau.v$ ) has been altered. As seen previously the precision has been diminished in the BYM model, but also in the model including the urban/rural indicator which is the most successful of the models with potential covariates. The precision of the spatially correlated heterogeneity term is the same in the models except for that including the mean radon measurement which diminishes it.

Figure 91 Posterior estimates for non postcode specific parameters in BYM models



### 5.7.2 Conclusions of Inclusion of Covariates

Therefore a number of issues have been highlighted by the inclusion of these potential covariates to the two Bayesian models. The results from the DIC and the comparison of posterior estimates from the models indicate that the variation in the relative risks testicular cancer within postcode sectors might be associated with the rural/urban indicator and the mean radon measurement of that area. The inclusion of these two covariates improved the Log-Normal model. This improvement was not replicated in the inclusion of covariates within the BYM model. However, from the comparison of the spatial variation of the heterogeneity terms and the changes in the parameters estimates it would appear that the inclusion of the spatially correlated heterogeneity soaks up any extra variation which we want to explain.

## 5.8 Summary of Testicular Cancer analysis

It is inconclusive that there is a spatial variation in the relative risk of testicular cancer in Scotland. The estimates produced by the Log-Normal and Poisson-Gamma model showed no spatial correlation. However the relative risk estimates produced by the BYM model appeared to show spatial correlation – low relative risks in urban areas and high ones in relatively rural areas. This spatial variation in the relative risk might be accurate; the BYM model was the best of the three models when comparing DIC results and so might best describe the spatial correlation of the relative risks. However, there are indications that the spatially correlated heterogeneity term might over-smooth the spatial correlation of the relative risk estimates where none exists.

The performance of the BYM model is also highlighted when the potential covariates were included to explain the extra variation in the relative risks. The inclusion of the rural/urban indicator and the mean radon measurement improved the Log-Normal model and so might explain the variation in the relative risks. However the inclusion of these covariates in the BYM model did not improve the model. With further assessment of the posterior estimates of the different BYM models it would appear that although there is an association between these two covariates and the relative risks the inclusion of the spatially correlated heterogeneity soaks up the extra variation we wish to account for.

Therefore, in general there might be a slight spatial correlation of the relative risks of testicular cancer within Scotland, although it is not a strong spatial variation. The variation in relative risks appears to be associated with the rurality and mean radon measurement of the area.



## Chapter 6 : Hypospadias Analysis

### 6.1 Introduction

This chapter details the analysis of the hypospadias dataset. As the hypospadias data has been analysed as disease count data only, the chapter has a similar format as the previous testicular cancer analysis chapter.

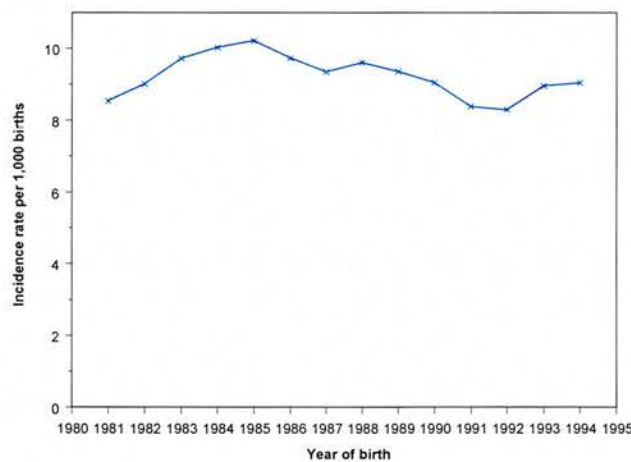
### 6.2 Summary of hypospadias dataset

As with the testicular cancer data, there has not been a spatial analysis of the individual covariates from the hypospadias data. However the summary carried out for the cryptorchidism cases is repeated here for the hypospadias data for comparison purposes, as both are congenital anomalies and originate from the same dataset,.

#### 6.2.1 Incidence over time

Unlike both the cryptorchidism and testicular cancer cases, the hypospadias incidence has not increased over time (Figure 92). It would appear that after an increase in the incidence for the first third of the time period of the hypospadias dataset, the incidence has fallen since with a slight increase for the last few years of the interval.

**Figure 92** Hypospadias incidence rate per 1,000 births (3 year moving average)



6.2.2 Mothers’ year of birth

The distribution of the mother’s year of birth for the hypospadias cases is similar to the cryptorchidism cases (Figure 93). The mother’s of the hypospadias cases had a year of birth ranging from 1937 to 1979 and mean of 1960, compared to 1935 to 1978 (mean 1960) for the mothers’ of the cryptorchidism cases.

Figure 93 Histogram of Mothers’ Year of Birth

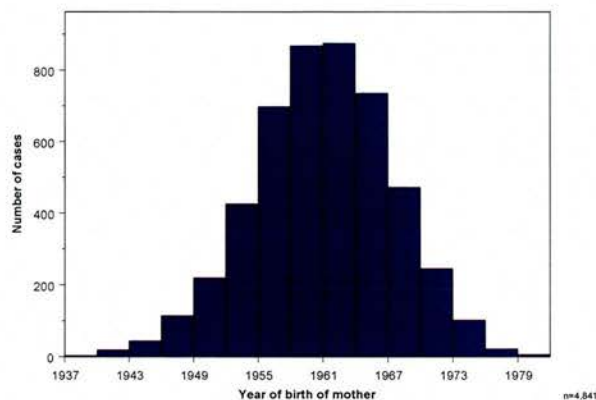
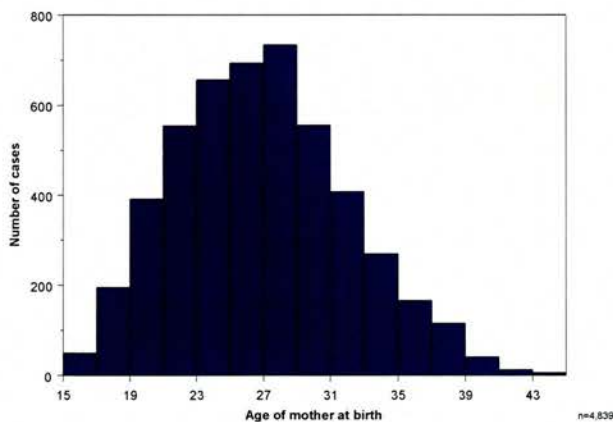


Figure 94 shows the distribution of the mothers’ ages of the hypospadias cases. Again the distribution is similar to the cryptorchidism cases. The range of the mothers’ age of the hypospadias cases is 15 to 43 with a mean of 26.4 years, compared to 14-45, mean 26.5 years for the cryptorchidism cases.

Figure 94 Histogram of mother’s age at son’s birth



So even though the hypospadias incidence over time is different from the cryptorchidism cases, this cannot be explained by differences in the mothers’ of these cases.

### 6.3 Standardised Morbidity Ratio (SMR) maps

The following gives the results of these calculations in relation to the hypospadias dataset.

#### 6.3.1 Observed number of hypospadias cases per 1991 postcode sector

Of the 4,919 cases of hypospadias, 25 records did not have postcode sector recorded. Therefore 4,894 cases were linked to the database created that matches all valid postcode sectors to where this would have been in 1991 (detailed in 3.5). Of the 801 postcode sectors within the hypospadias dataset, only 777 were linked to records within the 1991 database. The remaining 24 postcode sectors were not valid postcode sectors; and are detailed in Table 37.

**Table 37    Description of invalid postcodes in hypospadias dataset**

Description of invalid postcode sector	Number of postcode sectors (number of cases of hypospadias)
Mistyped postcode sector	5 postcode sectors (6 cases)
English postcode sector	3 postcode sectors (6 cases)
Local Council code	16 postcode sectors (226 cases)

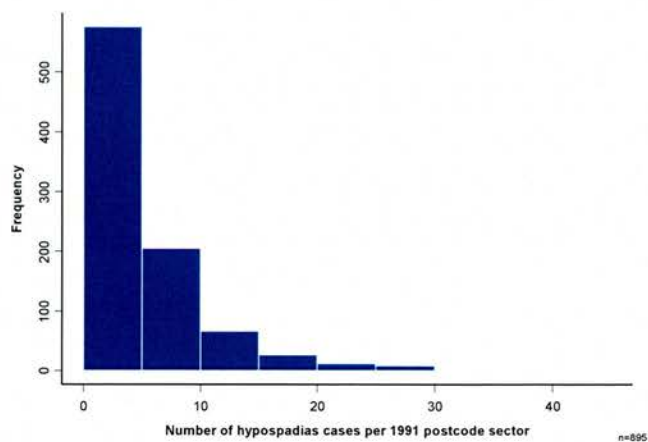
Of those postcode sectors mistyped, 4 (5 cases) could be corrected. However none of the remaining postcode sectors could be geographically referenced resulting in 233 cases being excluded from further analysis. This was valid for those cases with English postcode sectors, which probably resulted from cross-boundary attendance at a maternity hospital.

However, as with the cryptorchidism dataset a high number of cases were lost because particular hospitals have used local council codes instead of postcode sectors - Kirkcaldy (97 cases), North East Fife (16 cases) and Dunfermline (93 cases). This has the same impact on the analysis as discussed with the cryptorchidism dataset.

Therefore of the 4,919 cases of hypospadias 4,661 could be assigned to a 1991 postcode sector. The distribution of the number of cases within each of these postcodes sectors is shown in Figure 95.



**Figure 95   Histogram of the number of hypospadias cases per 1991 postcode sectors**



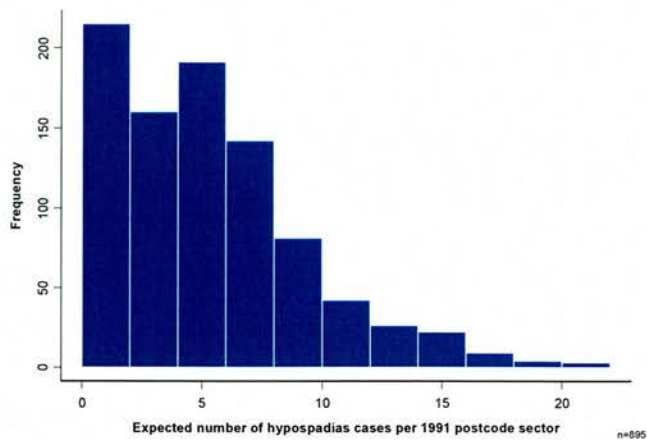
As can be seen the distribution is highly skewed - the number of cases in each postcode sector ranges from 0 to 43 with a median of 4 cases. Comparing the hypospadias values to the other two conditions, there is a wider range of hypospadias cases than found for either cryptorchidism (0-19) or testicular cancer (0-18) datasets, and has a higher median (cryptorchidism – 2; testicular cancer – 3). Therefore it has the highest incidence of the three conditions.

**6.3.2 Expected number of hypospadias cases per 1991 postcode sector**

The expected numbers of hypospadias cases per 1991 postcode sector were standardised by year of birth and the underlying population used was all births.

The distribution of the expected number of hypospadias cases within each of the 1991 postcode sectors is shown in Figure 96. While the distribution is skewed it is not as wide a range of values as those observed for hypospadias – 0-21.4 compared to 0-43. Furthermore the median expected value (4.73) is larger than the median observed (4) while their mean values are similar (5.3 expected; 5.2 observed), therefore the expected distribution does not appear to be as skewed as the observed. These differences in the distributions of the expected and the observed values are also comparable to the other two conditions within the research project.

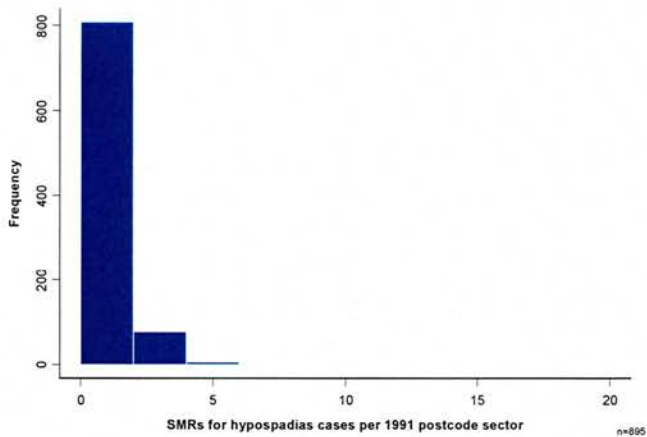
**Figure 96** Histogram of the expected number of hypospadias cases per 1991 postcode sectors



**6.3.3 SMRs of hypospadias per 1991 postcode sector**

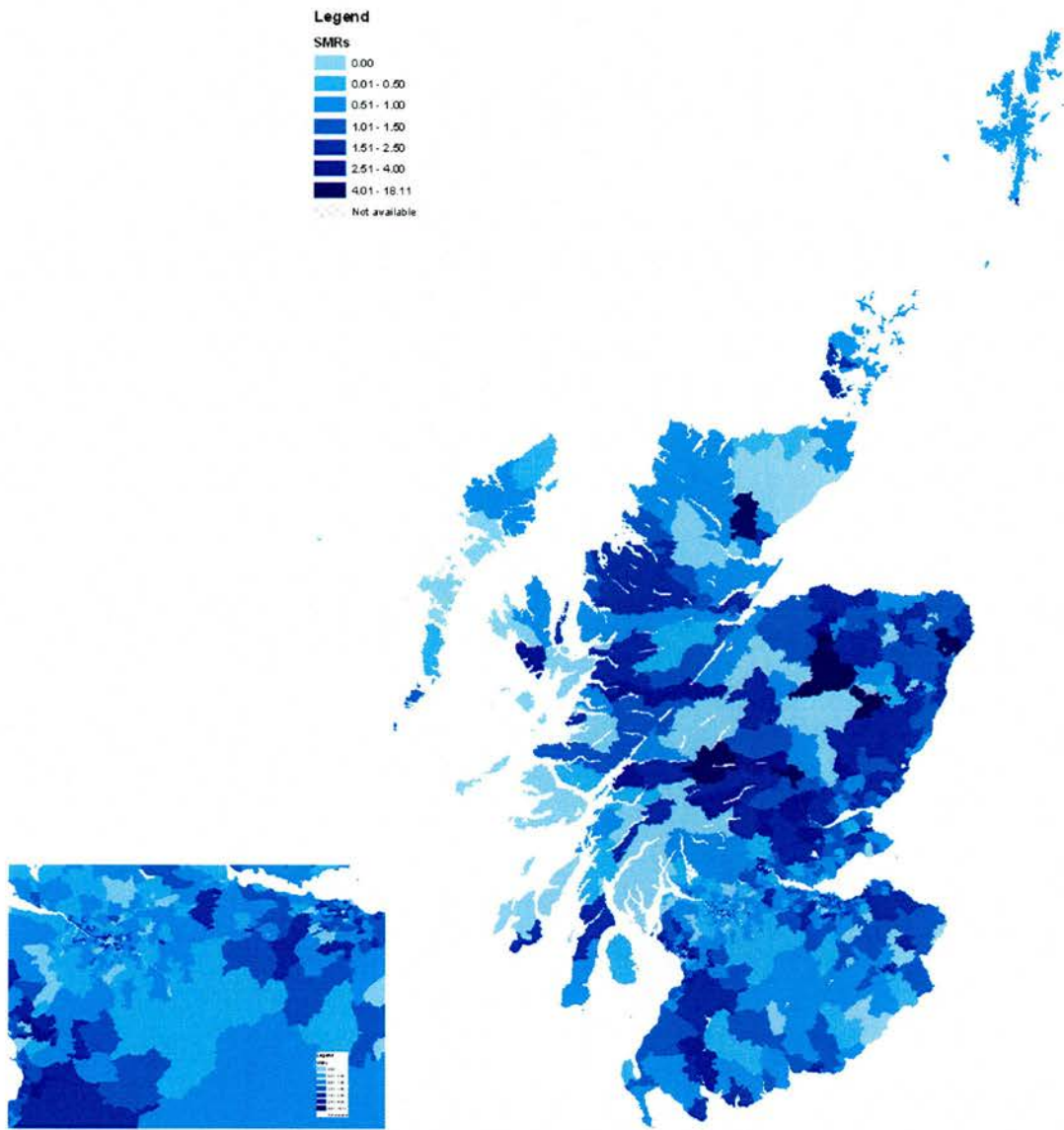
The distribution of the hypospadias SMRs for the 1991 postcode sectors is skewed; the maximum SMR is 18.11, the third quartile is 1.39, mean SMR is 0.98 (standard deviation 1.08) and the median is 0.82 (Figure 97).

**Figure 97** Histogram of hypospadias SMRs per 1991 postcode sector



Comparing the hypospadias SMRs with those for the other two conditions, all three have skewed distributions. While the hypospadias distribution is similar to the testicular cancer distribution (range 0-18.9; median 0.9), the cryptorchidism distribution has a longer tail (range 0-235.6; median 0.78).

There does appear to be a spatial pattern to the hypospadias SMRs across Scotland (Figure 98).

**Figure 98** Hypospadias SMRs per 1991 postcode sectors: Scotland 1980-1999

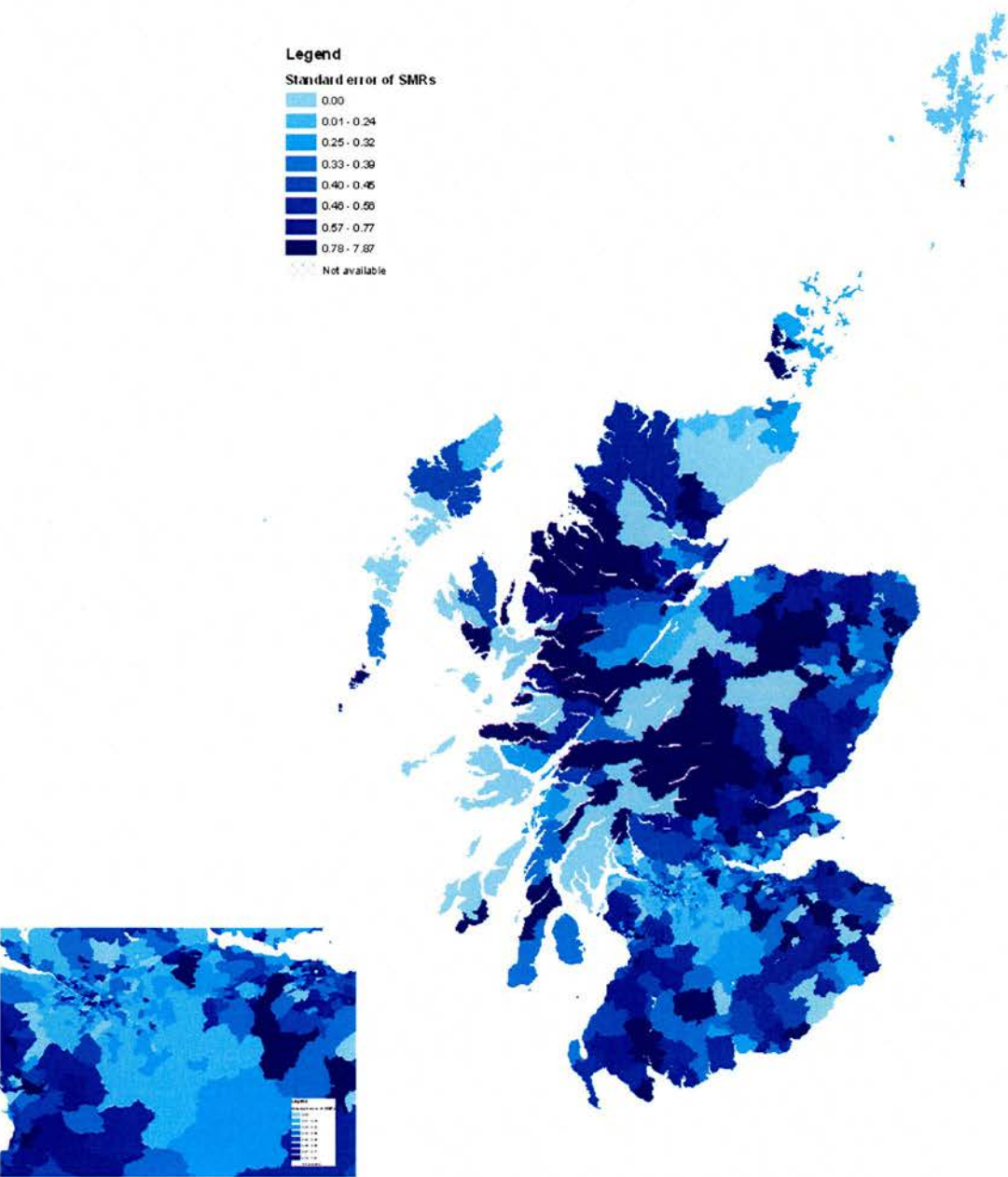
In particular, there does appear to be a cluster of higher relative risk in the east and south-west of Scotland and lower relative risks in the area from the central border to the west of Scotland.

The variability of the estimates of the SMRs can be assessed by the standard error of each SMR. The distribution of the standard errors is skewed – range 0-7.8, median 0.37 and mean 0.46. Compared to the other conditions the variability of the hypospadias standard errors of the SMRs is not as great (cryptorchidism 0-235.6, mean 0.92; testicular cancer 0-15.6, mean 0.58).



The spatial variation of the standard errors is similar in some areas to the SMRs i.e. the SMRs may reflect the random variation of the estimates rather than any variation in disease risk (Figure 99). Therefore it looks important to take into account this variability when calculating the hypospadias disease risk, which can be done with Bayesian models.

**Figure 99** Hypospadias standard error of SMRs per 1991 postcode sector: Scotland 1980-1999



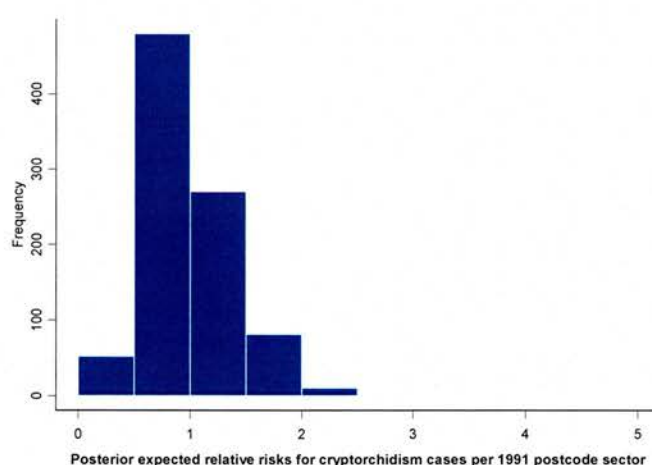
## 6.4 Bayesian hierarchical modelling of hypospadias data – Poisson-Gamma model

The Poisson-Gamma model was run with the hypospadias dataset in WinBUGs which converged following 3,000 iterations, a further 10,000 were run to produce robust posterior estimates.

### 6.4.1 Posterior estimates from model

The distribution of the hypospadias posterior expected relative risks for each of the 1991 postcode sectors as produced by the Poisson-Gamma model is shown in Figure 100.

**Figure 100 Histogram of Hypospadias posterior expected Relative Risk estimated from the Poisson-Gamma model**



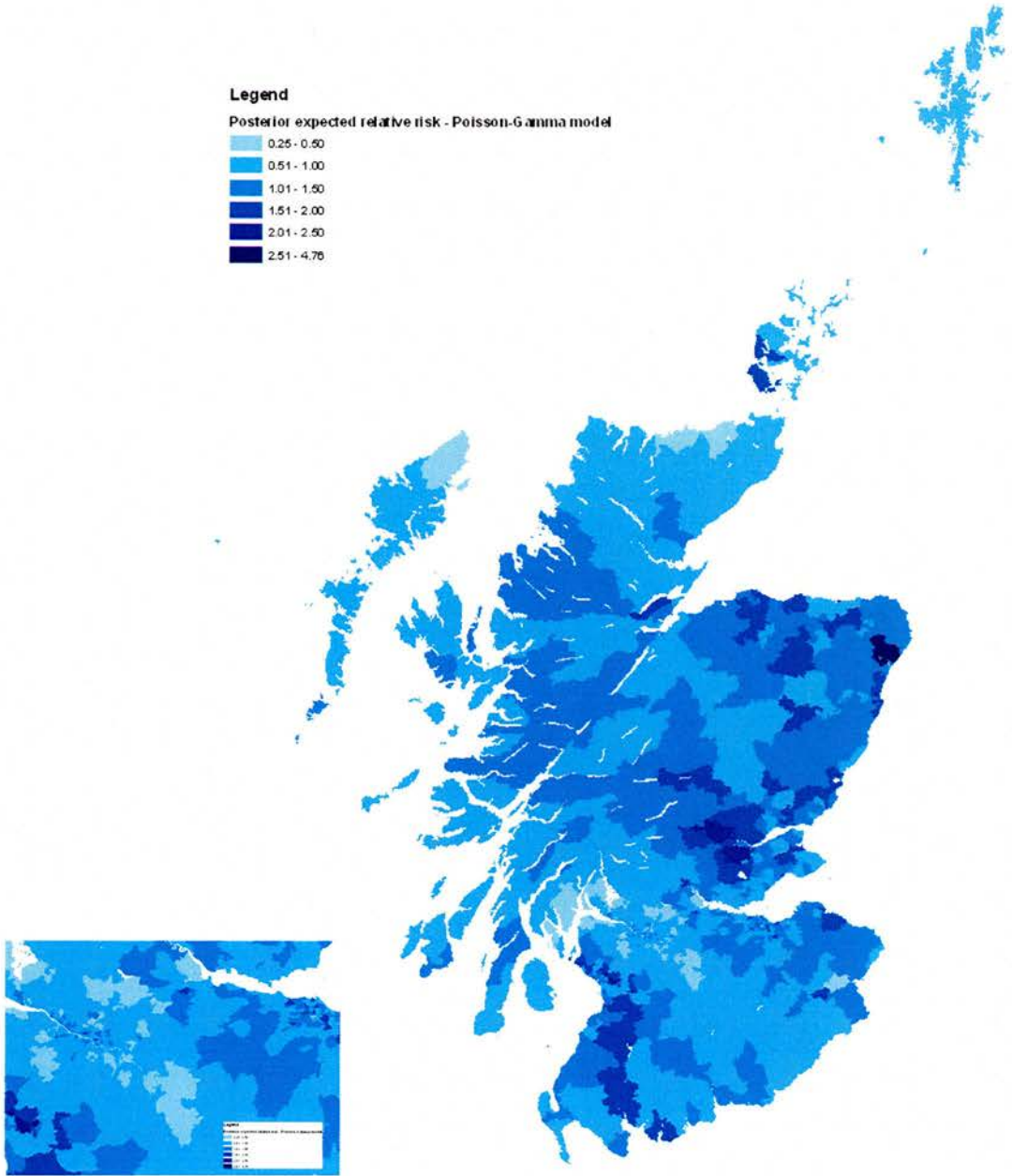
The distribution is less skewed than that for the SMRs (median 0.99 and mean 1.004) and the range of values has been reduced (0.25, 4.76) towards the population mean relative risk of 1.006 (Table 38). As the standard deviation of the population mean relative risk is 0.02 then the variability of this estimate has been reduced compared to the SMR.

Compared to the spatial variation of the SMRs, the spatial pattern of the relative risks produced by the Poisson-Gamma is the same although smoothed (Figure 101).

Table 38 Posterior estimates for parameters in Poisson-Gamma model

Parameter	Mean	Standard Deviation	MC error	2.5% credible interval	Median	97.5% credible interval
a	3.386	0.3013	0.01915	2.844	3.369	4.018
b	3.369	0.3159	0.02012	2.801	3.354	4.039
mean	1.006	0.02563	4.81E-04	0.956	1.006	1.057
var	0.3013	0.0316	0.001871	0.2442	0.2995	0.3673

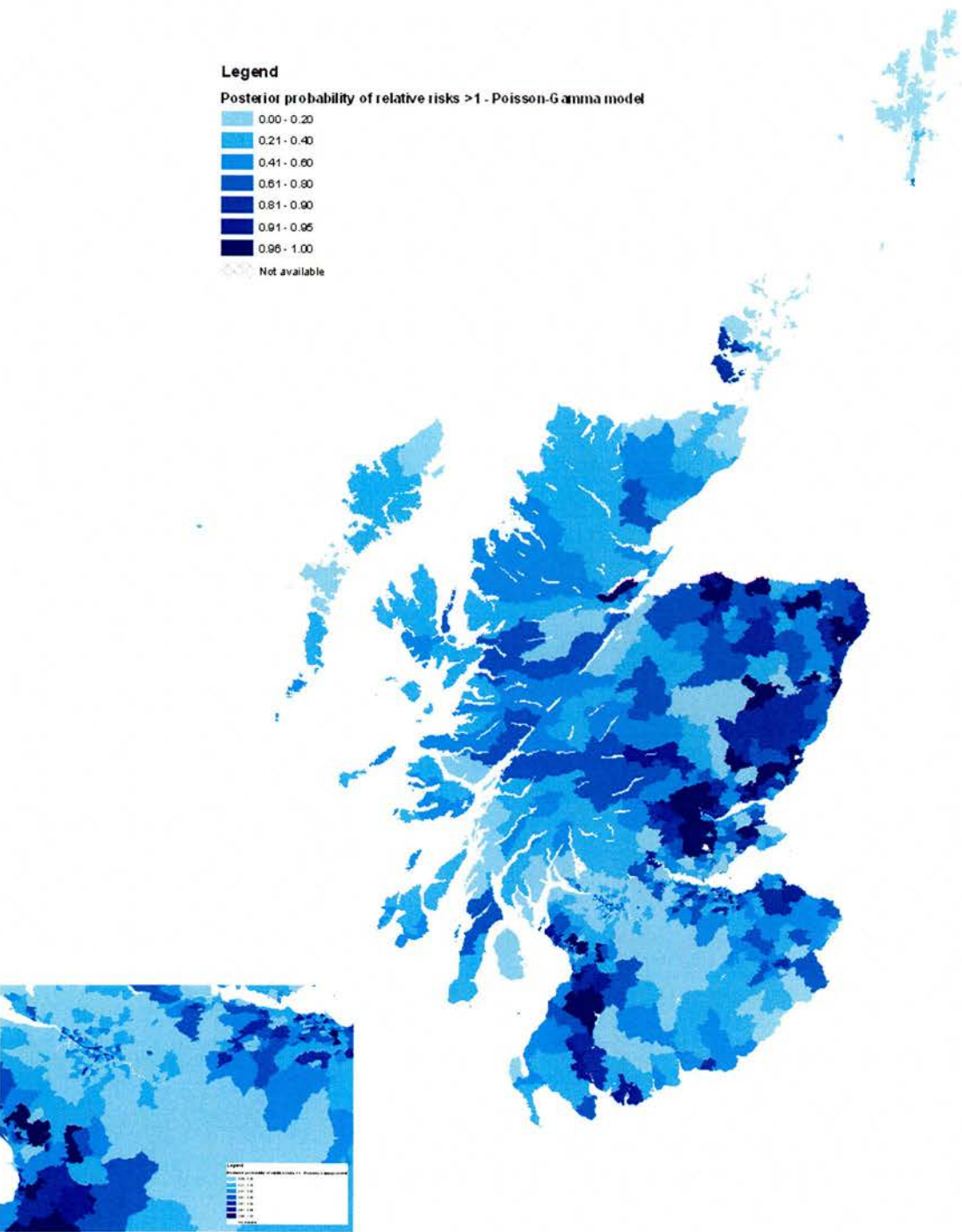
Figure 101 Hypospadias posterior expected relative risk per 1991 postcode sector from the Poisson-Gamma model: Scotland 1980-1999





The probabilities of the relative risks being greater than 1, show a similar spatial pattern to the relative risks map, so confirming the areas with high and low relative risk while taking into account the variability of the estimates (Figure 102).

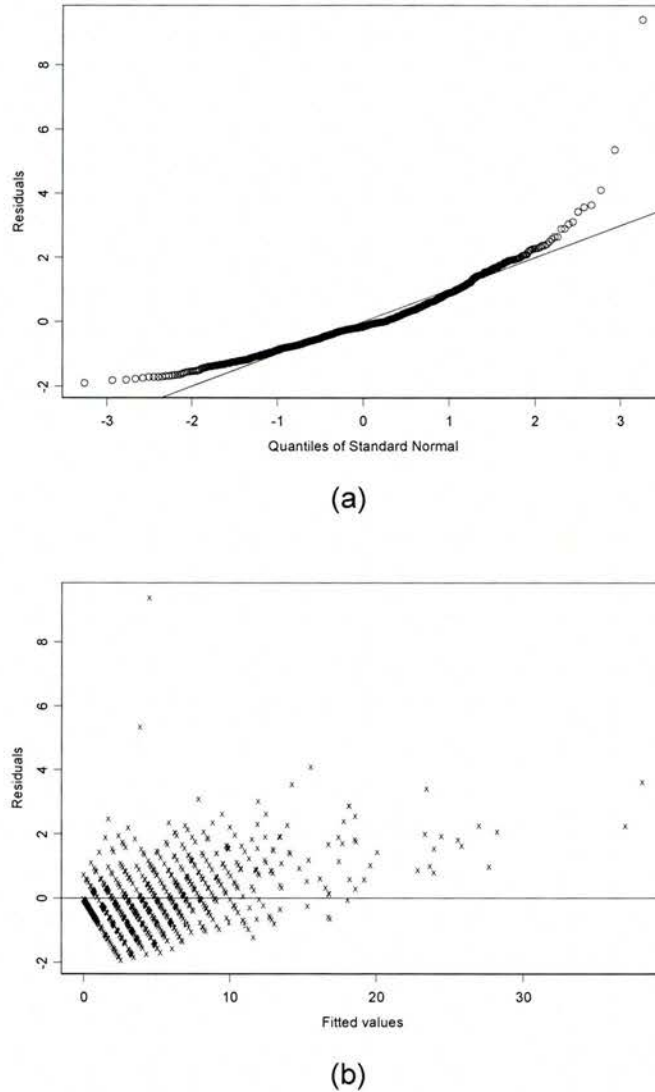
**Figure 102 Hypospadias Posterior probabilities for expected relative risk per 1991 postcode sector from the Poisson-Gamma model: Scotland 1980-1999**



### 6.4.2 Assessment of model

The analysis of the standardised residuals is shown in Figure 103.

**Figure 103 Poisson-Gamma Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted**

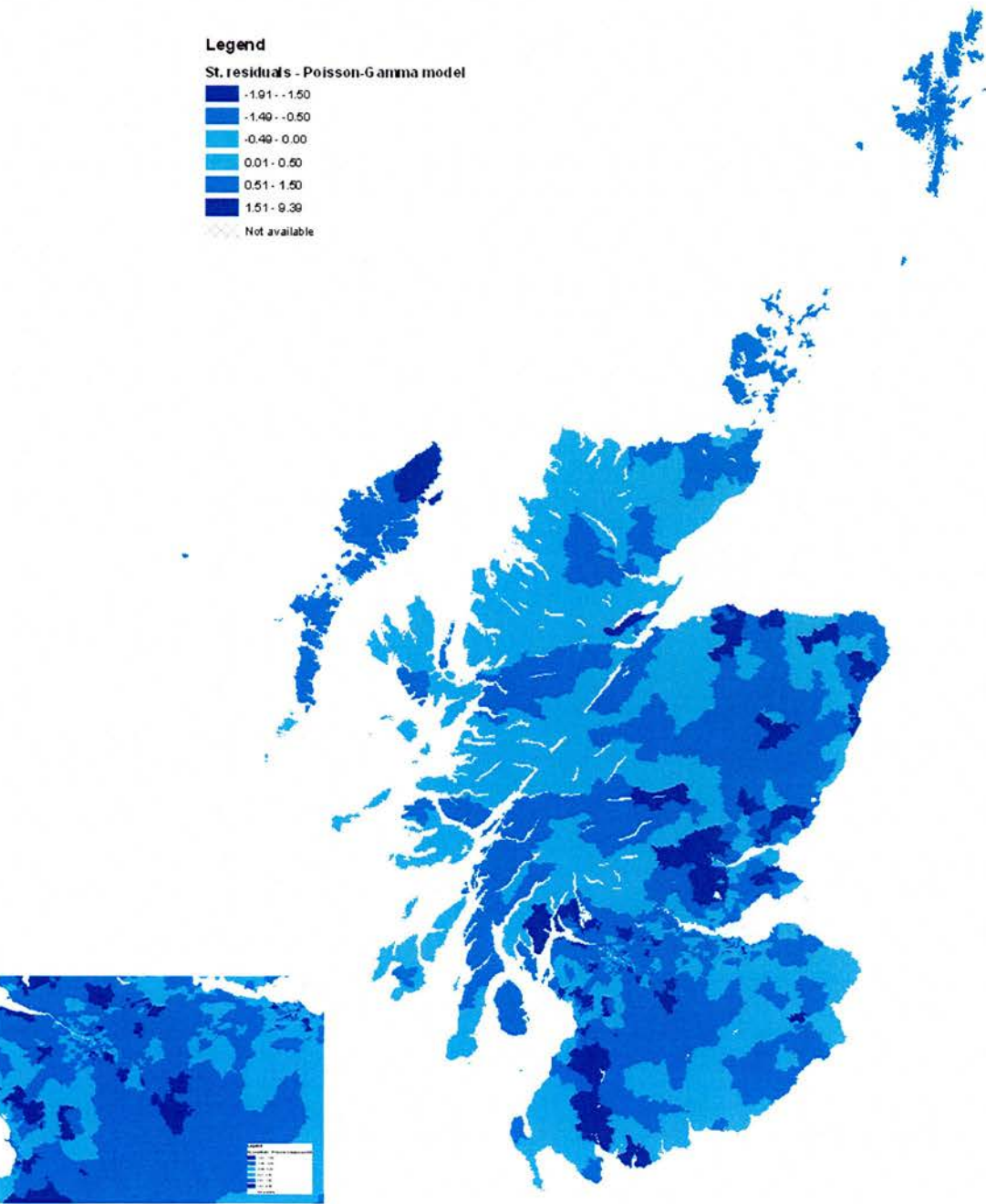


The Poisson-Gamma model is not an adequate fit to the hypospadias dataset. The normal plot (a) does not follow the x-y line, in particular the extreme values of relative risks. The residuals are not evenly scattered across all fitted values (b), again the larger fitted values appear to the least successful, although a number of small fitted value also appear to not fit the Poisson-Gamma model. Therefore, while the

Poisson-Gamma model appears to fit to those fitted values around the mean, it is unsuccessful at fitting the extreme values.

There is also spatial correlation of the residuals, in particular in the North-East of Scotland (Figure 104). So the Poisson-Gamma model does appear to the least successful in those areas with high relative risks.

**Figure 104** Hypospadias residuals of Poisson-Gamma model: Scotland 1980-1999





Furthermore, the Moran's I test shows that there is a statistically significant ( $p=4.03 \times 10^{-80}$ ) spatial correlation ( $r=0.4$ ) of the residuals (Table 39).

**Table 39 Moran's I test result for residuals from Poisson-Gamma model**

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.4 (0.35, 0.44)
Correlation Normal p-value (2-sided)	$4.03 \times 10^{-80}$
Mean Permutation correlations (Inter-quartile range)	0.0006 (-0.0120, 0.0136)
Permutation p-value	<0.0001

There is evidence that the residuals appear to cluster in areas where high relative risks are estimated, so the Poisson-Gamma model does not fully explain the variability of these estimates. It might be appropriate to include a term in any models that attempt to describe the spatial variation of hypospadias that accounts for the spatially correlated heterogeneity.

### 6.4.3 Conclusions for Poisson-Gamma model

The Poisson-Gamma model is not a complete appropriate fit to the hypospadias data. The model smoothes the relative risks, decreases the range of their values and so produces a smoother spatial pattern. However, it does not take into account the variability in the estimates, in particular those areas with high relative risks. This might be due to the model not taking into account spatial correlation i.e. that a postcode sector will be similar to its neighbours.

## 6.5 Bayesian Hierarchical Models of hypospadias count data – Log-Normal

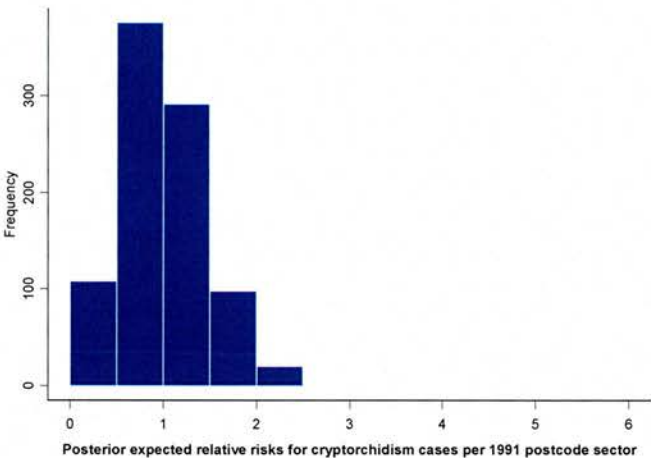
The Log-Normal model was run with the hypospadias dataset in WinBUGs and converged following 2,000 iterations. To produce robust posterior estimates a further 10,000 iterations were run.

### 6.5.1 Posterior estimates from model

The distribution of the hypospadias posterior expected relative risks for each of the 1991 postcode sectors as produced by the Log-Normal model is shown in Figure 105. While the distribution is similar to that for the relative risks produced by the Poisson-Gamma model, the range of relative risks produced is wider (0-5.92) than

those from the Poisson-Gamma (0.25-4.76). The distribution of relative risks is less skewed (median 0.96 and mean 0.99) for the Log-Normal compared to the Poisson-Gamma model (median 0.99 and mean 1.004).

**Figure 105 Histogram of Hypospadias posterior expected Relative Risk estimated from the Log-Normal model**



Therefore, the Log-Normal model smooths the relative risk estimates towards the population mean relative risk (0.87 standard deviation 0.02 (Table 40).

**Table 40 Posterior estimates for parameters in Log-Normal model**

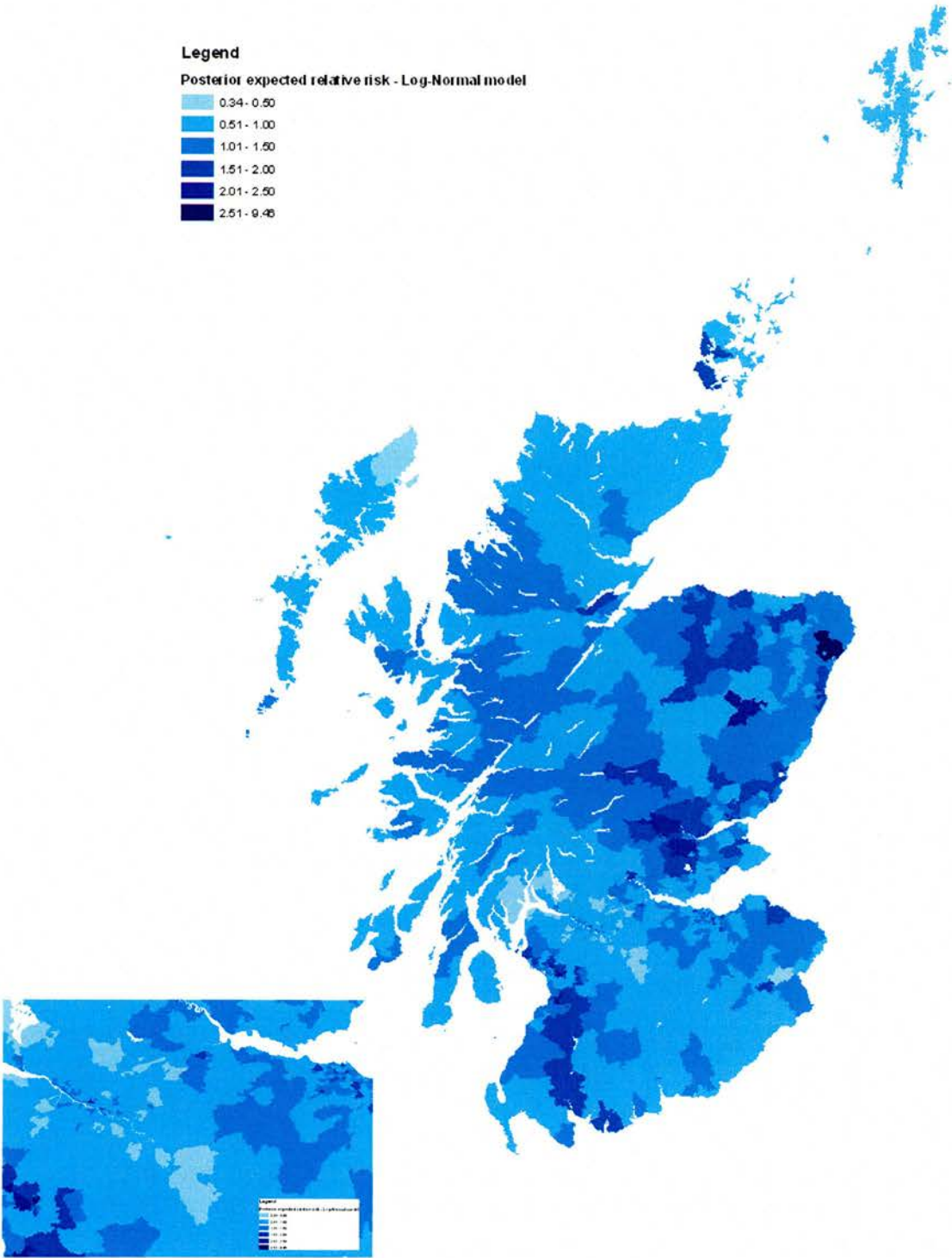
Parameter	Mean	Standard Deviation	MC error	2.5%	Median	97.5%
alpha	-0.1372	0.02694	6.01E-04	-0.1906	-0.1372	-0.08533
mean	0.8721	0.02348	5.24E-04	0.8265	0.8718	0.9182
tau.v	3.476	0.3156	0.006938	2.901	3.463	4.137

While this is a reduction in the range of relative risks compared to the SMRs, it not to the same extent as those produced by the Poisson-Gamma model. Furthermore, the population mean relative risk produced by the Log-Normal is much lower than that produced by the Poisson-Gamma model (1.006) and the SMRs (0.98). And the variability of this estimate has been reduced compared to the SMR and to the same extent as that done by the Poisson-Gamma model.

The spatial variation of the relative risk estimates produced by the Log-Normal model is very similar to that produced by the Poisson-Gamma model (Figure 106). Again we can see two regions with an elevated hypospadias risk in the East and

South-West of Scotland, and an area with a reduced risk from the central Borders to the West of Scotland.

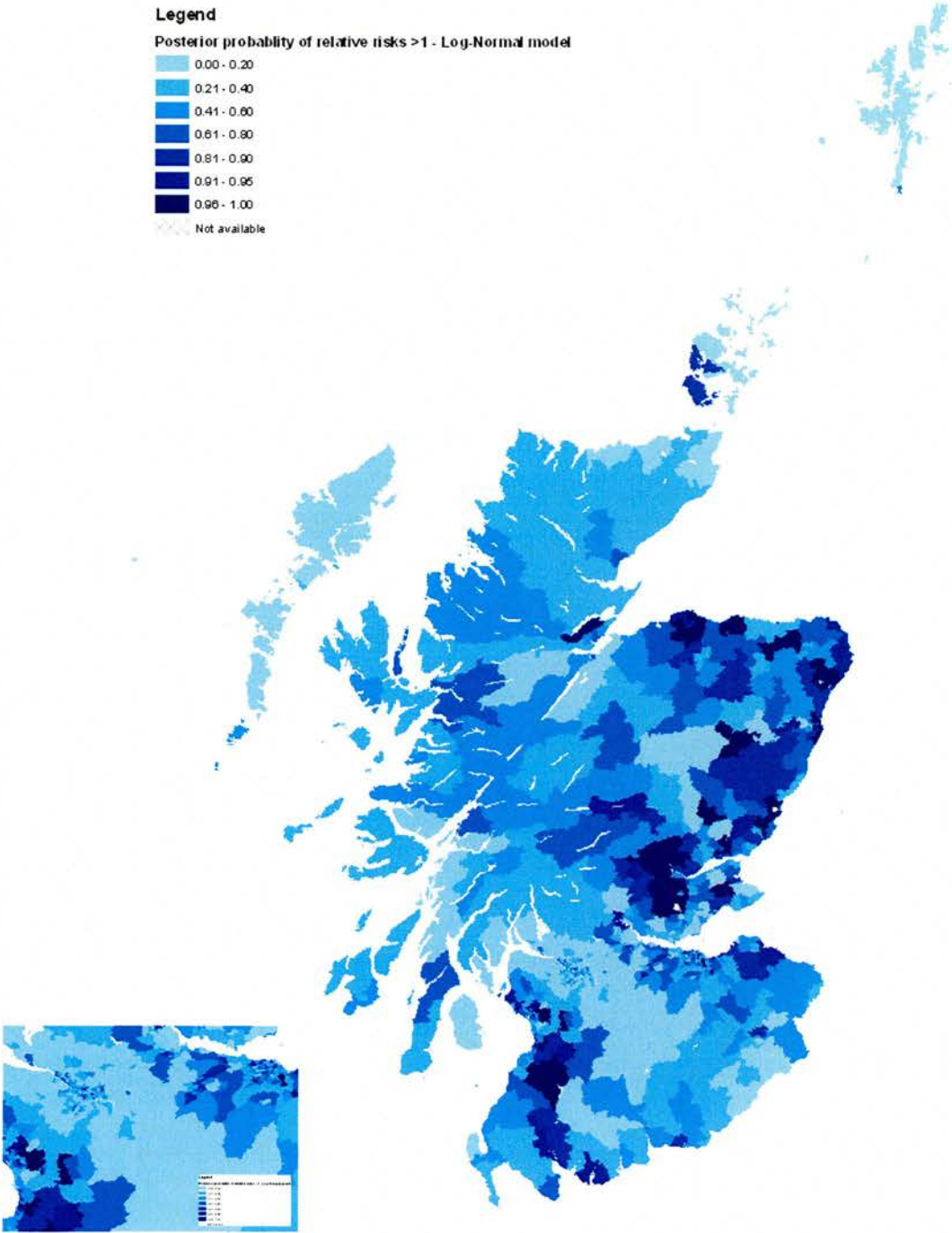
**Figure 106** Hypospadias posterior expected relative risk per 1991 postcode sector from the Log-Normal model: Scotland 1980-1999





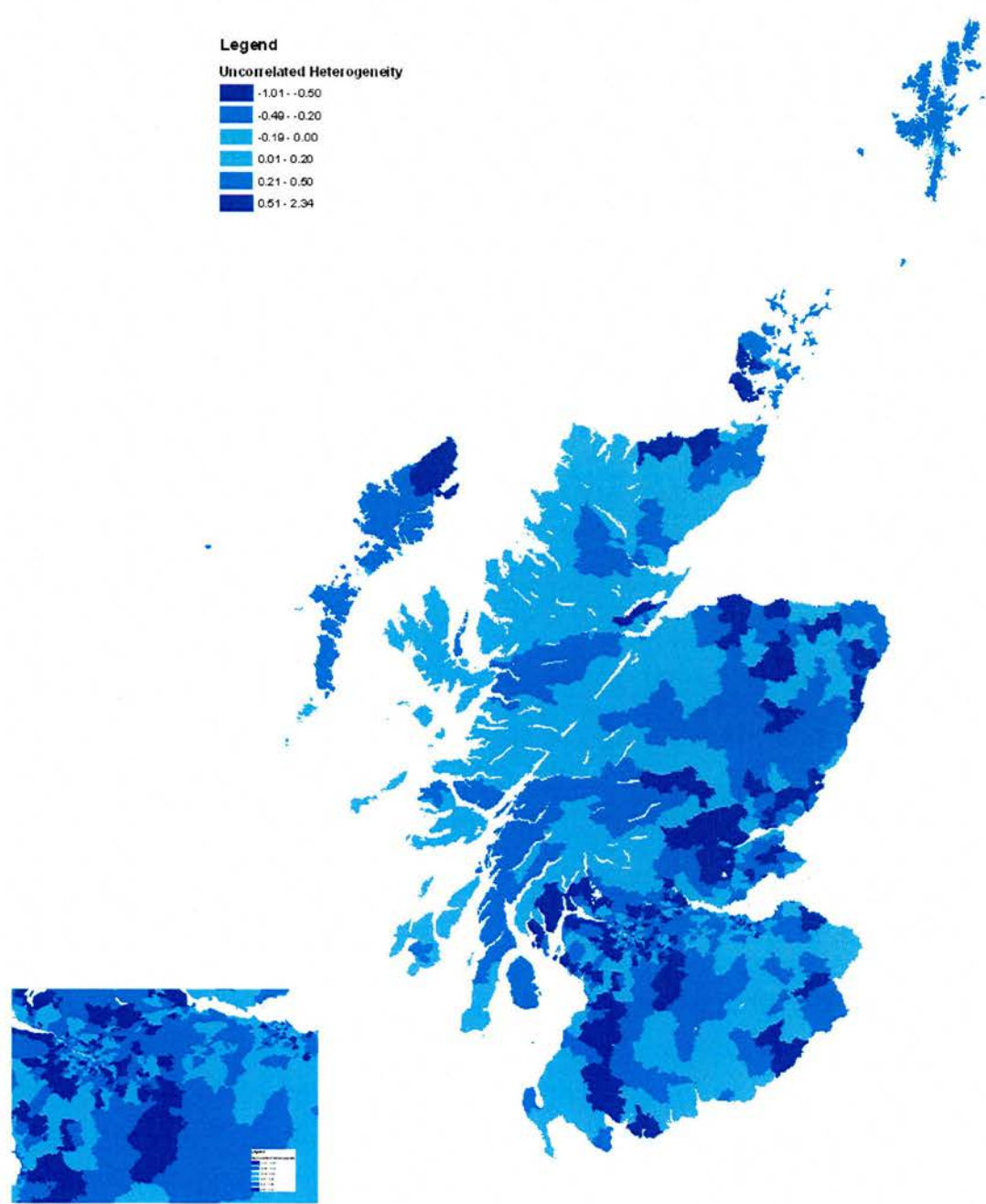
The probabilities of the relative risks being greater than 1, show a similar spatial pattern to the relative risks map, so confirming the areas with high and low relative risk while taking into account the variability of the estimates (Figure 107).

**Figure 107** Hypospadias posterior probability of relative risk being greater than 1 per 1991 postcode sector from the Log-Normal model: Scotland 1980-1999



The map of the uncorrelated heterogeneity term from the Log-Normal model shows that those areas with high relative risks also have high extra variation (Figure 108). This provides some evidence that the heterogeneity of the relative risks appear to vary in a spatially structured way.

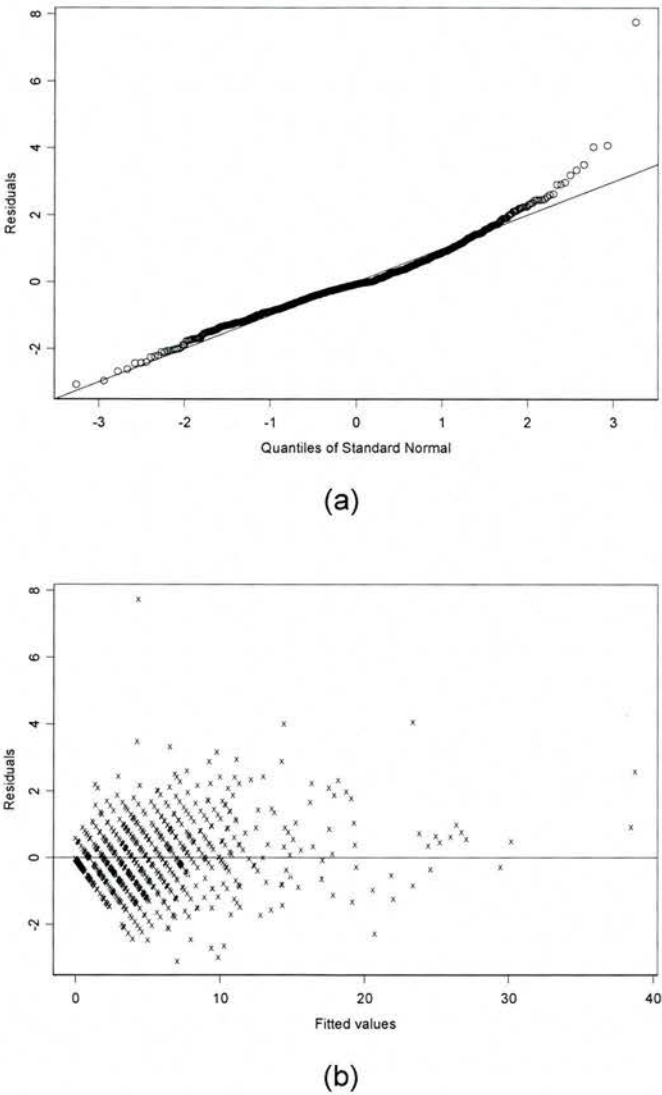
**Figure 108** Hypospadias posterior probability of uncorrelated heterogeneity per 1991 postcode sector from the Log-Normal model: Scotland 1980-1999



6.5.2 Assessment of model

The analysis of the standardised residuals produced for each relative risk estimate from the Log-Normal model is shown in Figure 109.

Figure 109 Log-normal Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted

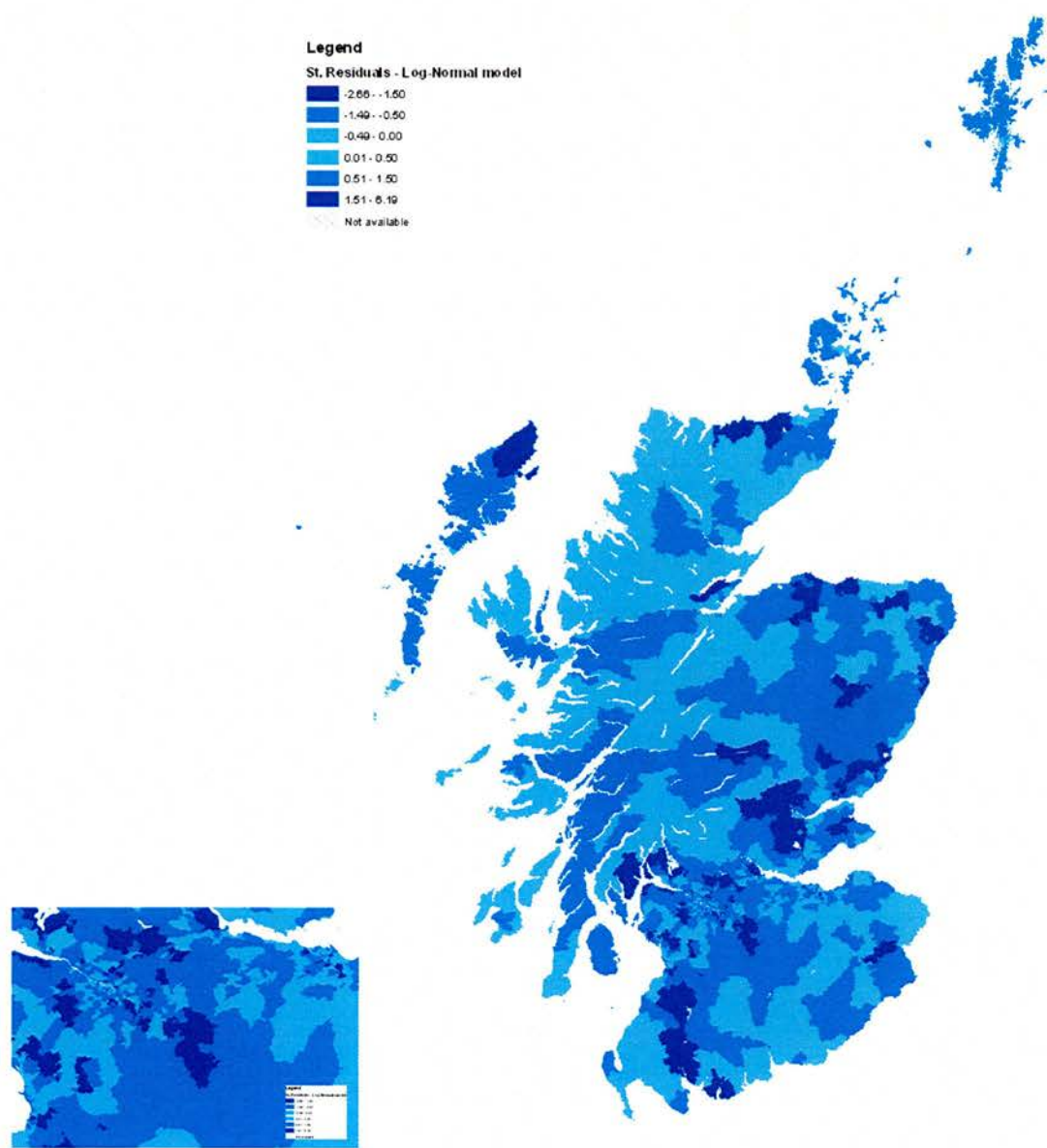


The Log-Normal fits the hypospadias dataset better than the Poisson-Gamma model, although it is still not completely appropriate for the higher relative risks. The normal plot (a) shows the residuals follow the x-y line better than those from the Poisson-Gamma model; in particular the lower values now follow the line. However the higher relative risks still do not fit the model as well as the other values. The



residuals are more evenly scattered across all fitted values than the Poisson-Gamma residuals (b), however again the larger fitted values appear not to follow this pattern. The spatial variation of the residual produced by the Log-Normal model is similar to those produced by the Poisson-Gamma model i.e. spatial correlation of high residuals values in the North-East and South West of Scotland and lower residuals in the North-West and South-East (Figure 110). Therefore, as with the Poisson-Gamma model, the Log-Normal model does not successfully account for the heterogeneity in those areas with high relative risks of hypospadias.

**Figure 110** Hypospadias residuals of Log-Normal model: Scotland 1980-1999



From Table 41, there is a statistically significant ( $p < 0.001$ ) correlation of the residuals, although it is a small negative one ( $r = -0.083$ ). Furthermore, the permutation correlation is not statistically significant at the 95% level. Therefore it is inconclusive that there is spatial correlation of the residuals.

**Table 41    Moran’s I test result for residuals from Log-Normal model**

Statistic	Result
Number of permutations	100
Correlation (95% CI)	-0.083 (-0.124, -0.062)
Correlation Normal p-value (2-sided)	$9.85 \times 10^{-5}$
Mean Permutation correlations (Inter-quartile range)	-0.004 (-0.0196, 0.0125)
Permutation p-value	1

**6.5.3 Conclusions for Log-Normal model**

The Log-Normal model is a slight improvement on the Poisson-Gamma model for estimating the relative risks for the hypospadias dataset. The same spatial variation of the disease risk was found i.e. higher risk in East and South-West of Scotland with lower risk in the region between the Central Borders and West of Scotland. And, like the Poisson-Gamma model, there was some evidence of spatial correlation of the residuals, so neither model fully explained the variability of the high relative risk estimates. However, from the residual analysis the Log-Normal model fitted the hypospadias dataset slightly better than the Poisson-Gamma model.

Finally, as there was some evidence that the heterogeneity was spatially correlated, a term should be include to accounts for this so as to fully describe the spatial variation of the hypospadias relative risks.

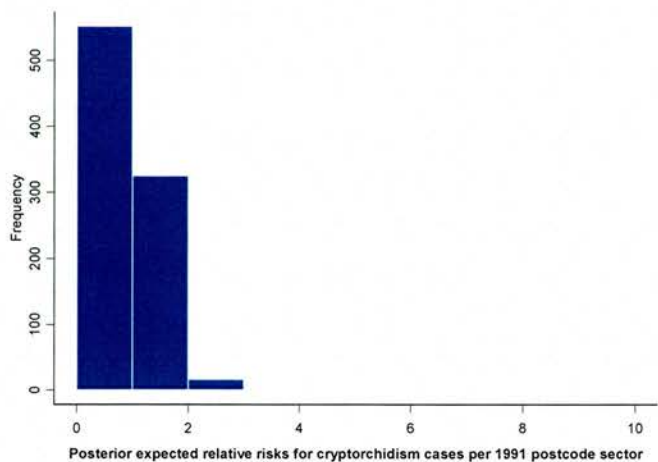
**6.6 Bayesian Hierarchical Models of cryptorchidism count data - Besag, York and Mollié (BYM) model**

The BYM model was run with the hypospadias dataset in WinBUGs and converged following 14,000 iterations. To produce robust posterior estimates a further 25,000 iterations were run.

**6.6.1 Posterior estimates from model**

Figure 111 shows the distribution of the posterior expected relative risks estimated by the BYM model.

**Figure 111 Histogram of Hypospadias posterior expected Relative Risk estimated from the BYM model**



The distribution of the estimates is very similar in shape to the SMRs i.e. skewed, although the range of values (0.34-9.46) is reduced compared to the SMRs (0-18.1). The BYM estimates have a higher maximum relative risk than both the Poisson-Gamma (4.76) and Log-Normal (5.92) but also a higher minimum (0.25 and 0 respectively), so it would appear that the distribution of the estimates has shifted to the right compared to the previous models.

As the distribution of the relative risk estimates produced by the BYM model is so skewed this has resulted in a population mean relative risks of 0.5, considerably lower than produced by SMRs or the other two Bayesian models (Table 42). Furthermore, the intercept term  $\alpha$  has increased, while the precision of the non-spatial heterogeneity term has deteriorated compared to the Log-Normal model. Therefore the inclusion of the spatially correlated heterogeneity term appears to have strengthened the intercept term but weakened the precision of the non-spatial heterogeneity.

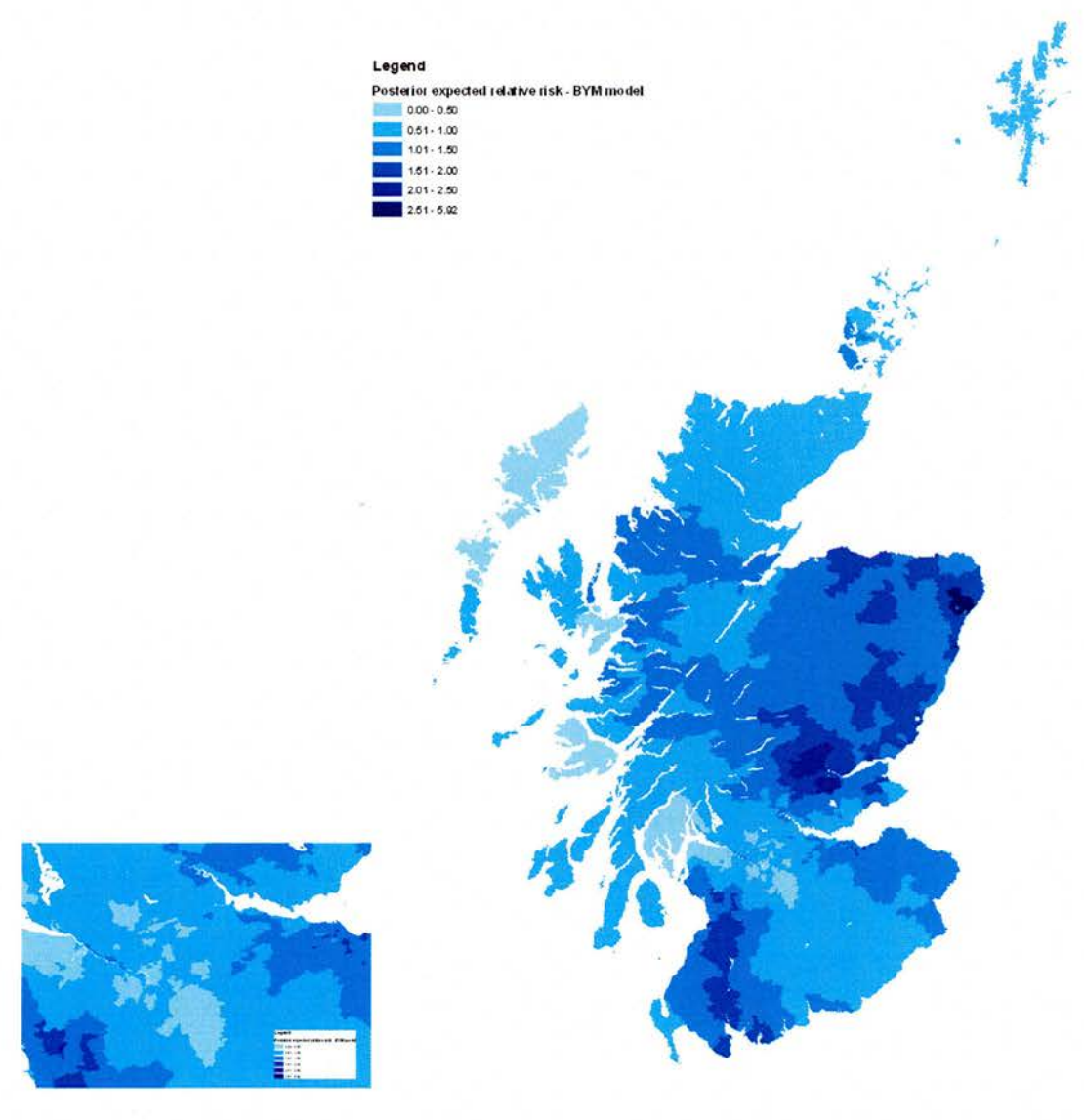


Table 42    Posterior estimates for non postcode specific parameters in BYM model

Parameter	Mean	Standard Deviation	MC error	2.5%	Median	97.5%
alpha	-0.7058	0.1612	0.0127	-0.9666	-0.7173	-0.4007
mean	0.5002	0.08219	0.006475	0.3804	0.4881	0.6699
tau.u	2.881	0.3735	0.009307	2.233	2.849	3.717
tau.v	1248	1235	87.65	114.8	893.6	4831

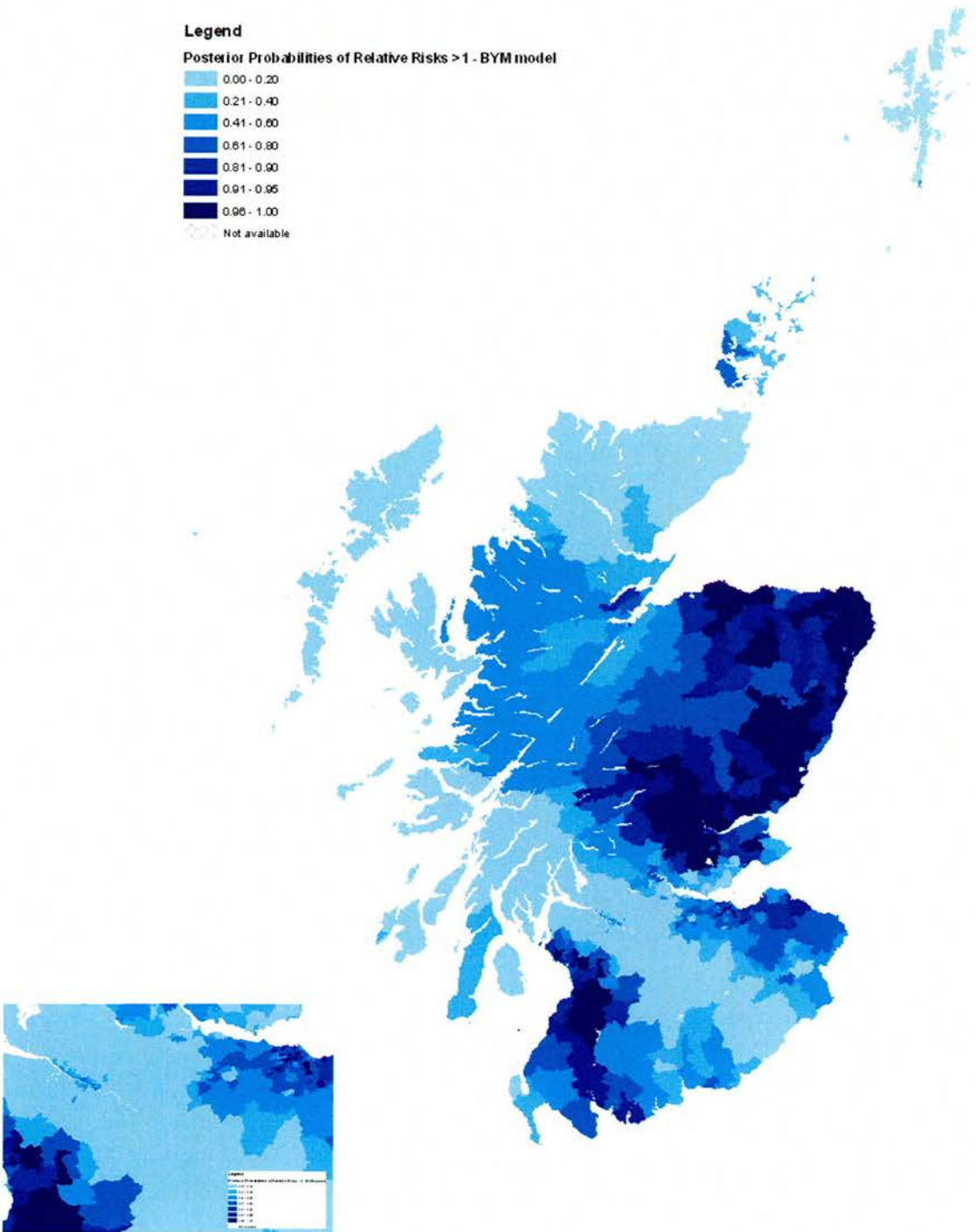
The spatial pattern of posterior expected relative risks from the BYM model is the same as that the Poisson-Gamma and Log-Normal models of the hypospadias dataset, although the pattern is more distinct (Figure 112).

Figure 112    Hypospadias posterior expected relative risk per 1991 postcode sector from the BYM model: Scotland 1980-1999



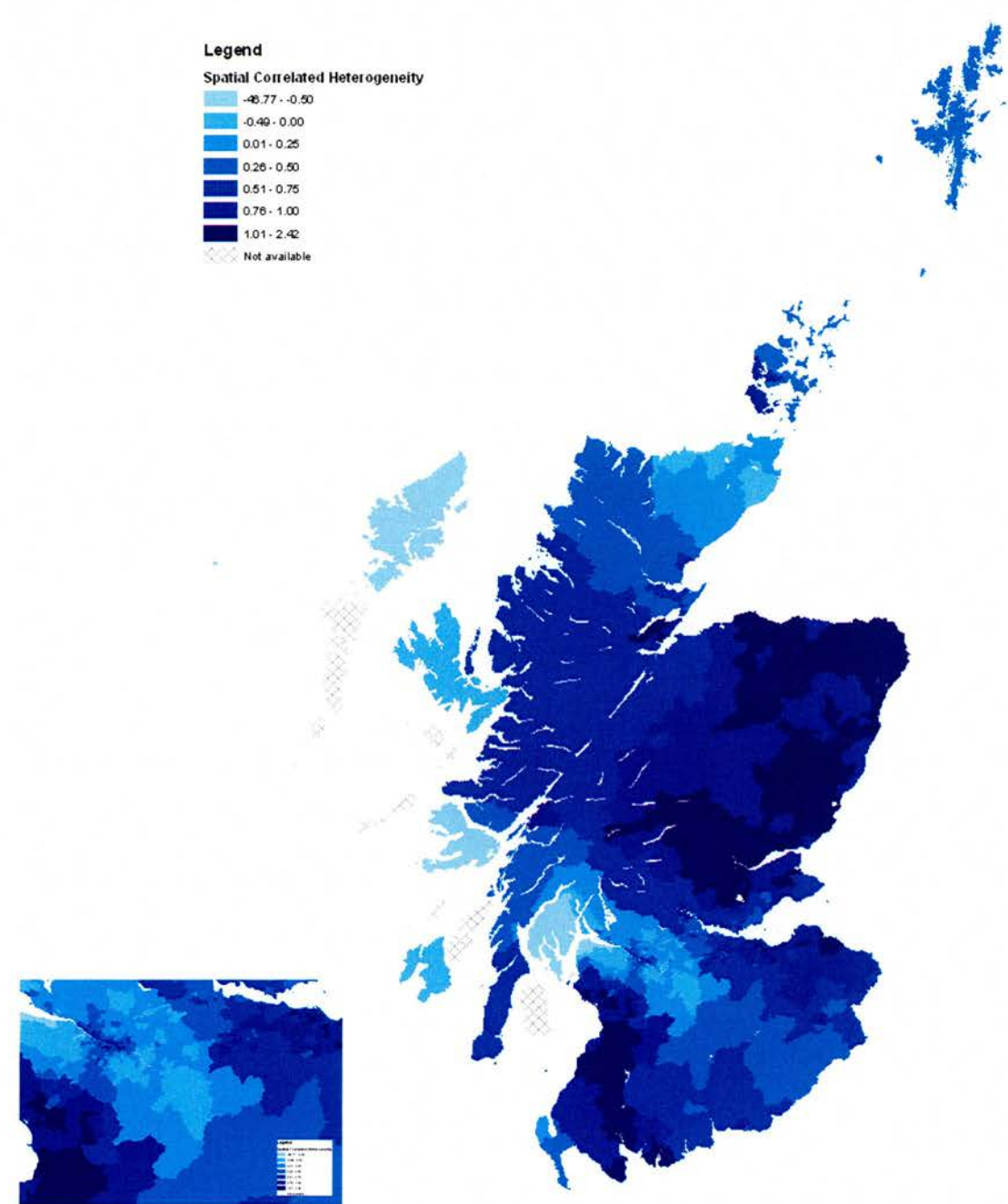
The probabilities of the relative risks being greater than 1 show a similar spatial pattern to the relative risks map, so confirming the areas with high and low relative risk while taking into account the variability of the estimates (Figure 113).

**Figure 113** Hypospadias posterior probabilities of expected relative risk per 1991 postcode sector from the BYM model: Scotland 1980-1999



The spatially correlated heterogeneity term in the BYM shows a similar spatial pattern as the BYM relative risk estimates (Figure 114). It would appear that the variability of the random effects has a spatial component, although this could be evidence of a strong spatial prior? Sensitivity analysis of the prior will be able to investigate this (6.6.2).

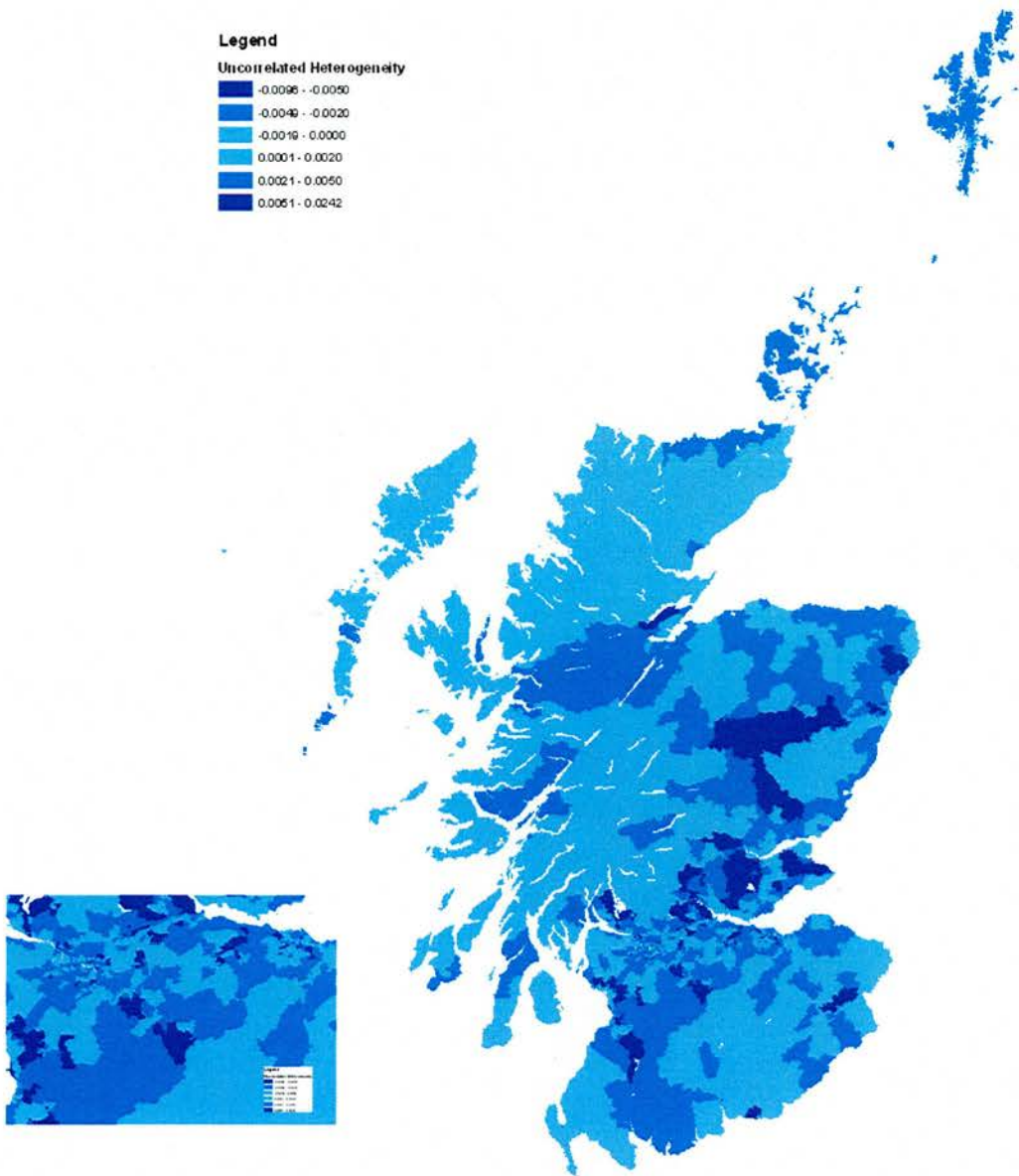
**Figure 114** Hypospadias posterior expected correlated Heterogeneity term  $u_i$  per 1991 postcode sector from the BYM model: Scotland 1980-1999





Furthermore, the spatial variation of the non-spatially correlated heterogeneity is not as distinct as produced in the Poisson-Gamma and Log-Normal models (Figure 115).

**Figure 115** Hypospadias posterior expected uncorrelated Heterogeneity term  $v_i$  per 1991 postcode sector from the BYM model: Scotland 1980-1999



This could be because the spatially correlated variability in the estimates of the relative risks found in the other two Bayesian models is now accounted for by the spatially correlated heterogeneity term. However, there is evidence that the CAR model used in the BYM model for the spatially correlated heterogeneity term over-smoothes the extra variation. For instance, the deterioration in the precision of the

non-spatially correlated heterogeneity term between the Log-Normal and BYM model.

6.6.2 Sensitivity Analysis

Table 43 shows the results of the comparison of the relative risks estimated by the BYM model outlined (Model 1) and those from the BYM model where the prior for tau.u is changed to gamma(0.5, 0.0005). There appears to be a strong correlation between the two sets of estimated relative risks, and no significant differences in the relative risks estimated for the same postcode sector. Therefore the distinct spatial pattern of the relative risks estimated by the BYM model is not due to the specific prior for the precision of the spatially correlated heterogeneity.

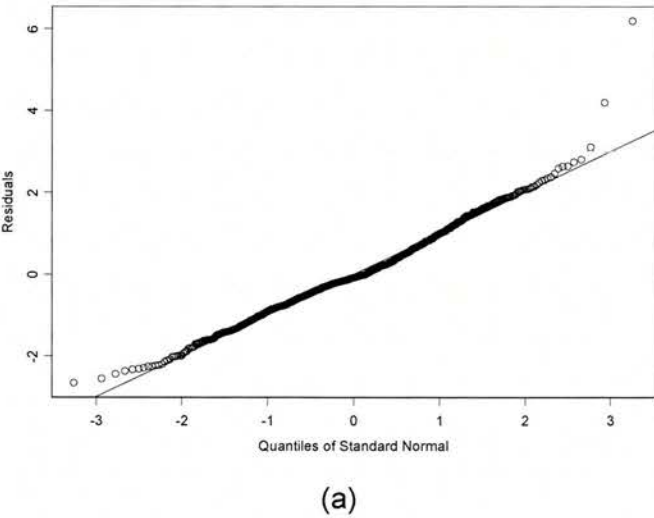
**Table 43** Comparison tests of Relative Risks estimated from BYM models using prior for tau.u gamma(1,1,) (model 1) and gamma(0.5, 0.0005) (model 2)

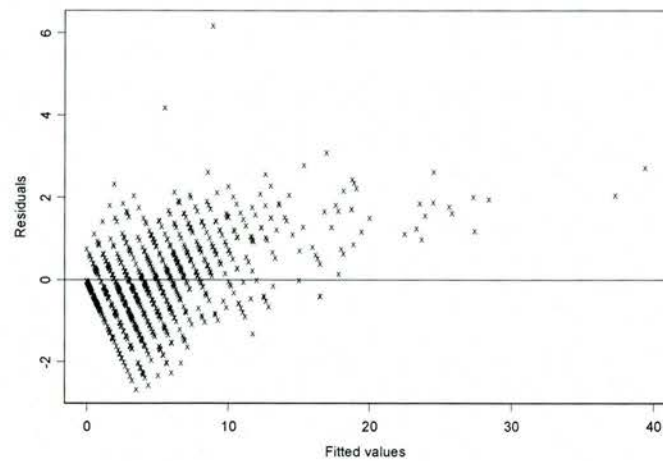
Correlation co-efficient of relative risks	Mean difference in relative risks (95% CI) (Model 1-2)	Paired t-test – p value
0. 9998	0. 0006 (-0.0002, 0.0013)	0. 1308

6.6.3 Assessment of model

The residual analysis for the BYM model is shown in Figure 116.

**Figure 116** BYM Model residuals analysis – (a) Normal Plot (b) Residuals v Fitted





(b)

It would appear that the BYM model is not any more successful than the other two Bayesian models. The Normal Plot of the residuals (a) does not follow the  $x=y$  line for the extreme values and the residuals are not evenly scattered when plotted by the fitted values (b), in a similar way to the Poisson-Gamma model.

There does appear to be some spatial correlation of the residuals, in particular in the North-East of Scotland (Figure 117).

From the Moran's I test results the spatial auto-correlation of the residuals is confirmed (Table 44). Therefore, as with the other models, the BYM model appears not to fully account for the heterogeneity in those areas with high relative risks



Figure 117 Hypospadias residuals of BYM model: Scotland 1980-1999

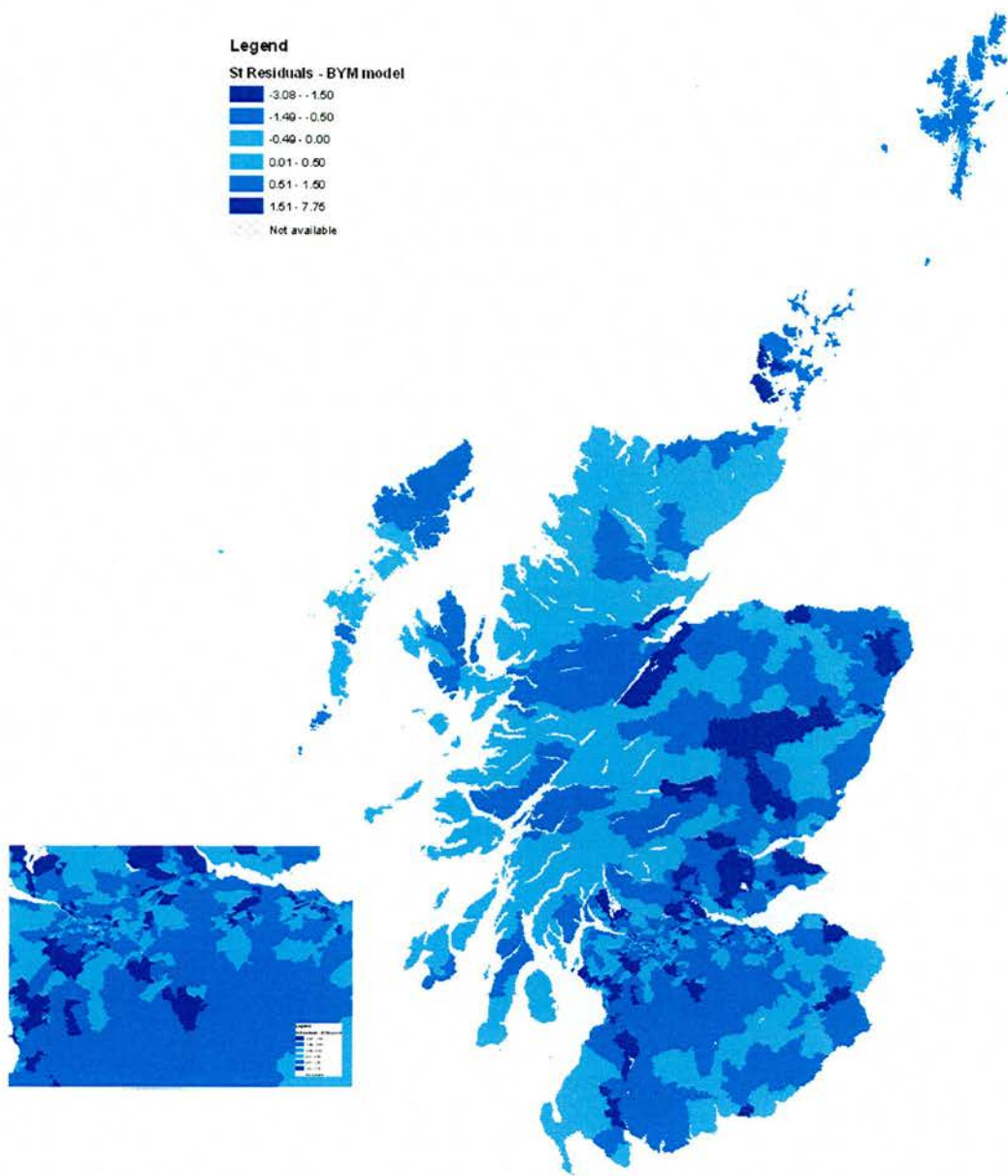


Table 44 Moran's I test result for residuals from BYM model

Statistic	Result
Number of permutations	100
Correlation (95% CI)	0.44 (0.40, 0.48)
Correlation Normal p-value (2-sided)	$4.23 \times 10^{-97}$
Mean Permutation correlations (Inter-quartile range)	-0.00046 (-0.01395, 0.01665)
Permutation p-value	<0.0001

It is possible to compare the DIC diagnostics of the three Bayesian Hierarchical models to assess which is the best fit to the hypospadias data (Table 45).

**Table 45    Model fitting results of the three disease count models**

Model	$\overline{D}$	$D(\overline{\mathcal{G}})$	pD	DIC
Poisson-Gamma model	3429.52	3002.63	426.894	3856.42
Log-Normal model	3443.48	3008.54	434.937	3878.41
BYM model	3397.67	3142.78	254.886	3652.55

From the DIC diagnostics, the BYM model fits the hypospadias dataset the best, with the Log-Normal model being the worst fit.

**6.6.4 Conclusions for BYM model**

It would appear that in general the BYM model is slightly better model and fit to the data compared to the Poisson-Gamma or Log-Normal model. However, it like the other two models is not successful in accounting for the spatial variation of the relative risks and the variability of their estimates.

**6.7 Inclusion of covariates into Bayesian hierarchical models of disease count data**

The inability of the three Bayesian models to fully account for spatial variation might not be due to the terms used within the models but that other explanatory variables might explain the spatial variation of the hypospadias relative risks. This section assesses if the inclusion of potential explanatory variables does help explain the increase risk in East and South-West Scotland and lower risk in the area from Central Border to the West of Scotland.

**6.7.1 Assessment of models**

Table 46 shows the different models ran in WinBUGs and the results for each of the DIC diagnostics.

**Table 46** Model fitting results of the Bayesian Hierarchical disease count models with covariates

Model	$\bar{D}$	$D(\bar{g})$	pD	DIC
1. Poisson-Gamma model	3429.52	3002.63	426.894	3856.42
2. Log-Normal model	3443.48	3008.54	434.937	3878.41
3. BYM model	3397.67	3142.78	254.886	3652.55
4. Log-Normal model plus deprivation (5 groups)	3443.04	3009.22	433.812	3876.85
5. Log-Normal model plus deprivation (7 groups)	3442.8	3008.38	434.418	3877.21
6. Log-Normal model plus urban/rural indicator	3456.01	3049.89	406.12	3862.13
7. Log-Normal model plus radon (mean)	4441.99	4440.02	1.974	4443.96
8. Log-Normal model plus radon (% >200)	3452.89	3044.10	408.792	3861.68
9. BYM model plus deprivation (5 groups)	3357.86	3041.89	315.967	3673.82
10. BYM model plus deprivation (7 groups)	3353.74	3030.32	323.422	3677.16
11. BYM model plus urban/rural indicator	3354.66	3033.81	320.85	3675.52
12. BYM model plus radon (mean)	3402.48	3150.93	251.55	3654.02
13. BYM model plus radon (% >200)	3354.47	3036.73	317.735	3672.2

The inclusion of the percentage of a region that has radon measurements greater than 200 Bq/m<sup>3</sup> or the rural/urban indicator explain some of the spatial variation in the hypospadias risk within the Log-Normal model. There is also some indication that deprivation might also improve the fit of the Log-Normal model, although it is not conclusive if we use a difference of 2 between DIC results as our threshold. However, when the spatially correlated heterogeneity is added to the models, as is the case in the BYM model, no model with the inclusion of potential covariates are an improvement on the basic BYM model. This conclusion is made from comparing DIC results; however, it would appear that the deviances are improved in the BYM model when all the covariates, except mean radon, are included. Therefore the data fits the hypospadias risk better with the inclusion of most of the covariates, but they are not better models when the number of parameters is taken into account. Could this be because the extra variation is soaked up by the spatially heterogeneity term and so could not be accounted for by the potential covariates? A comparison of the posterior estimates produced by these models might indicate what terms are accounting for the spatial variation in the hypospadias risk.

Figure 118 shows the relative risks produced by the six Log-Normal models described in Table 45. It would appear that the spatial variation is similar in most of



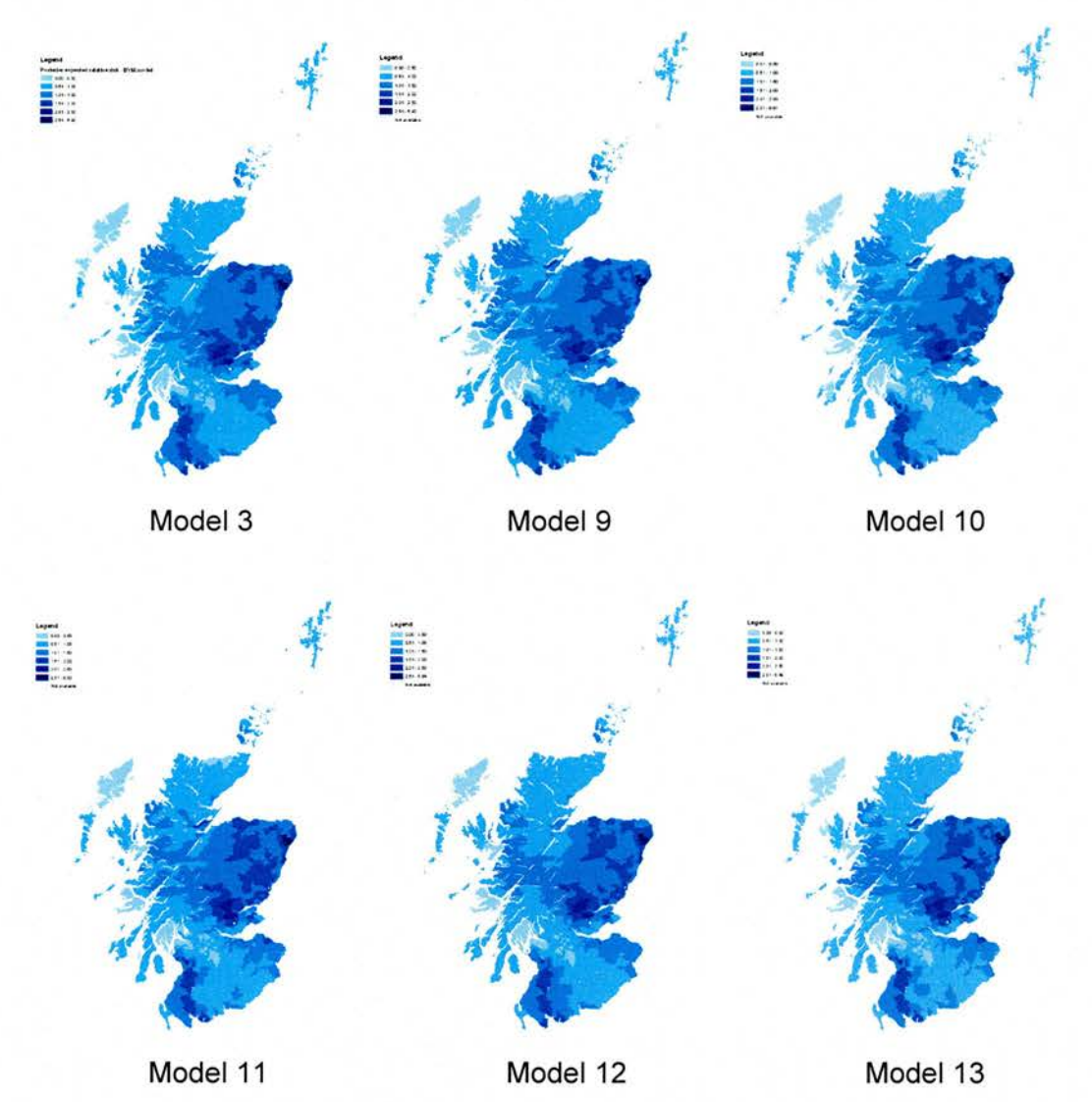
Log-Normal models although the values are altered by the particular covariate included. The spatial pattern of the relative risks the Log-Normal plus mean radon (model 7) is very different from the other models. The clustering of relative risks is much more distinct and also has a much narrower range of values (0.77-1.91). However the DIC result for this model is the worst for any model and so the poor fit of the hypospadias data to this model has probably produced this disparate spatial variation. For those two covariates (Models 6 and 8) where the DIC showed that they improved the Log-Normal model the relative risk values are reduced.

**Figure 118 Hypospadias posterior expected relative risk from Log-normal plus variable models**



Would the inclusion of the spatially correlated heterogeneity term to these models alter the spatial pattern of the relative risks? Figure 119 shows the relative risks produced by the six BYM models described in Table 45. All maps have the same categories and show the same spatial variation in hypospadias risk, even the BYM model with mean radon (model 12). Although there appears to be a reduction in the relative risk values produced in the BYM models that include the rural/urban indicator (Model 11) and the radon >200 (model 13) compared to the basic BYM model.

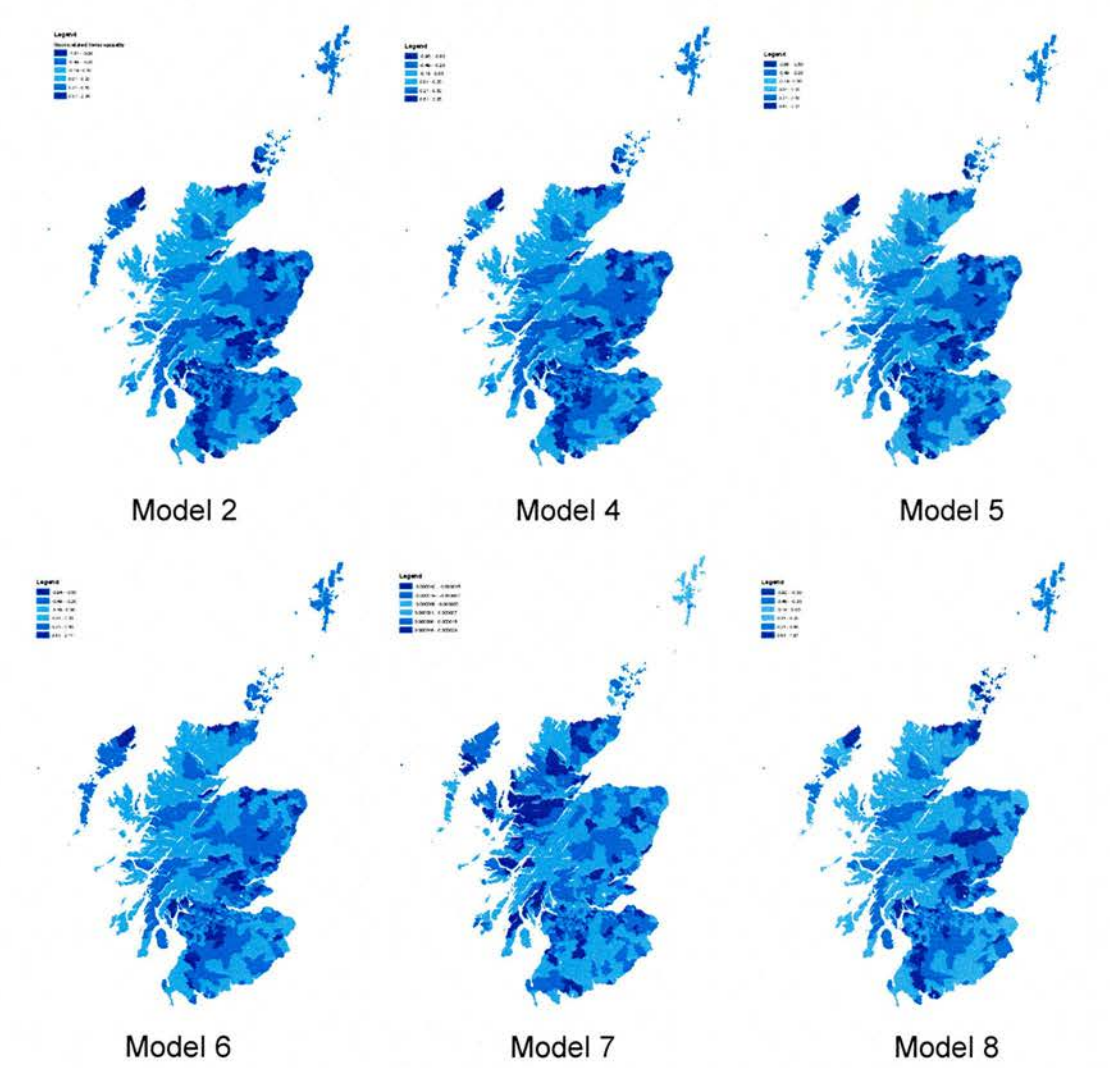
**Figure 119** Hypospadias posterior expected relative risk from BYM plus variable models





The spatial variation of the heterogeneity terms produced in the models might show what variation is accounted for with the inclusion of potential covariates. Again the spatial variation of the non-spatially correlated heterogeneity term is unaffected by the inclusion of covariates within the Log- Normal model, except in the model with mean radon included as a potential covariate (Figure 120 – Model 7). The pattern of the non-spatially correlated heterogeneity term is different in this model and the values are narrower. This could be as result of the poor fit of this covariate according to the DIC results. The random heterogeneity values are reduced in the Log-Normal models with the potential covariates that improve the model (Models 6 and 8). Therefore for those covariates that improve the Log-Normal model, the non random variability in the estimates of the relative risks is reduced.

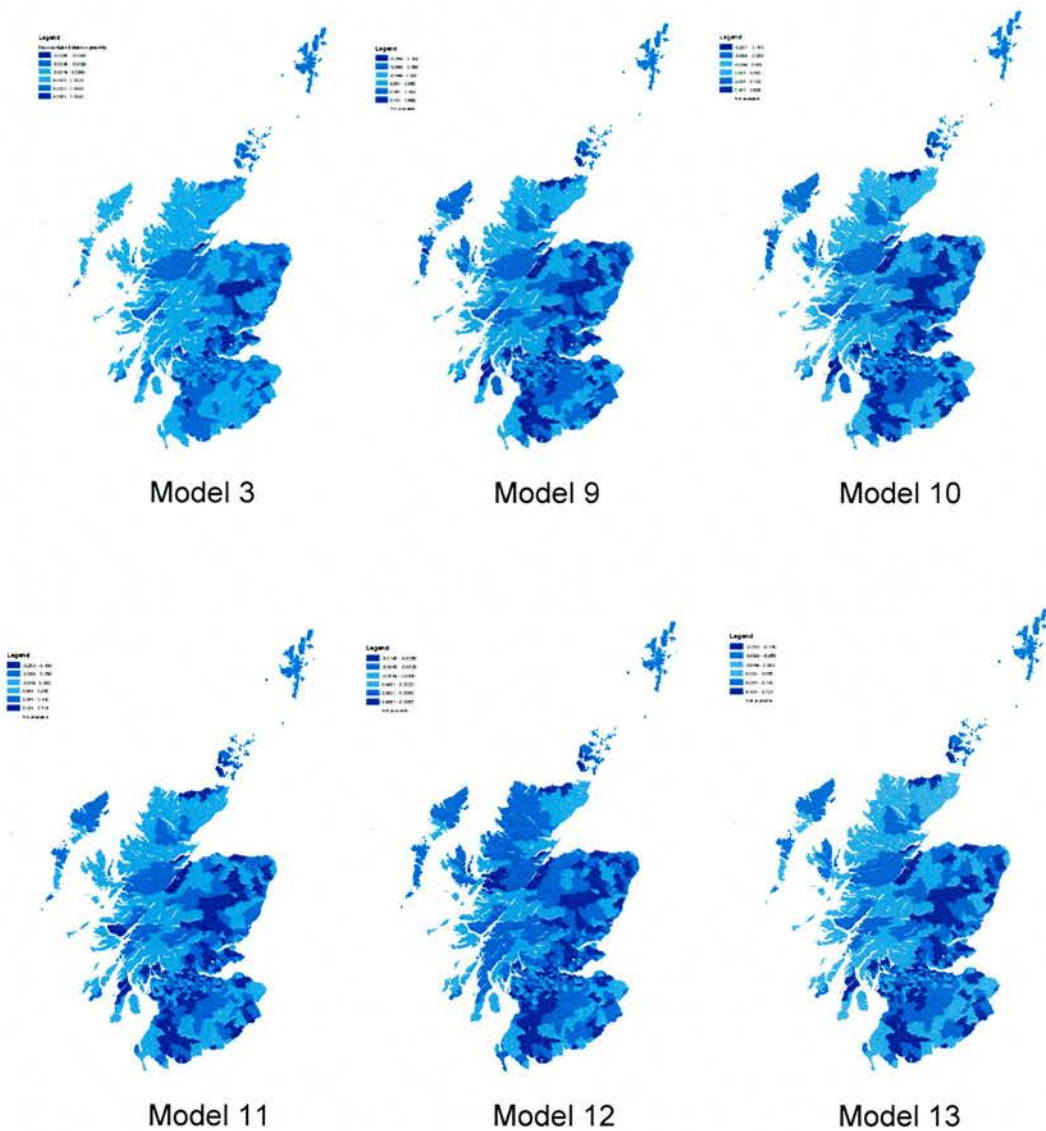
**Figure 120** Hypospadias posterior spatially uncorrelated heterogeneity term from Log-normal plus variable models





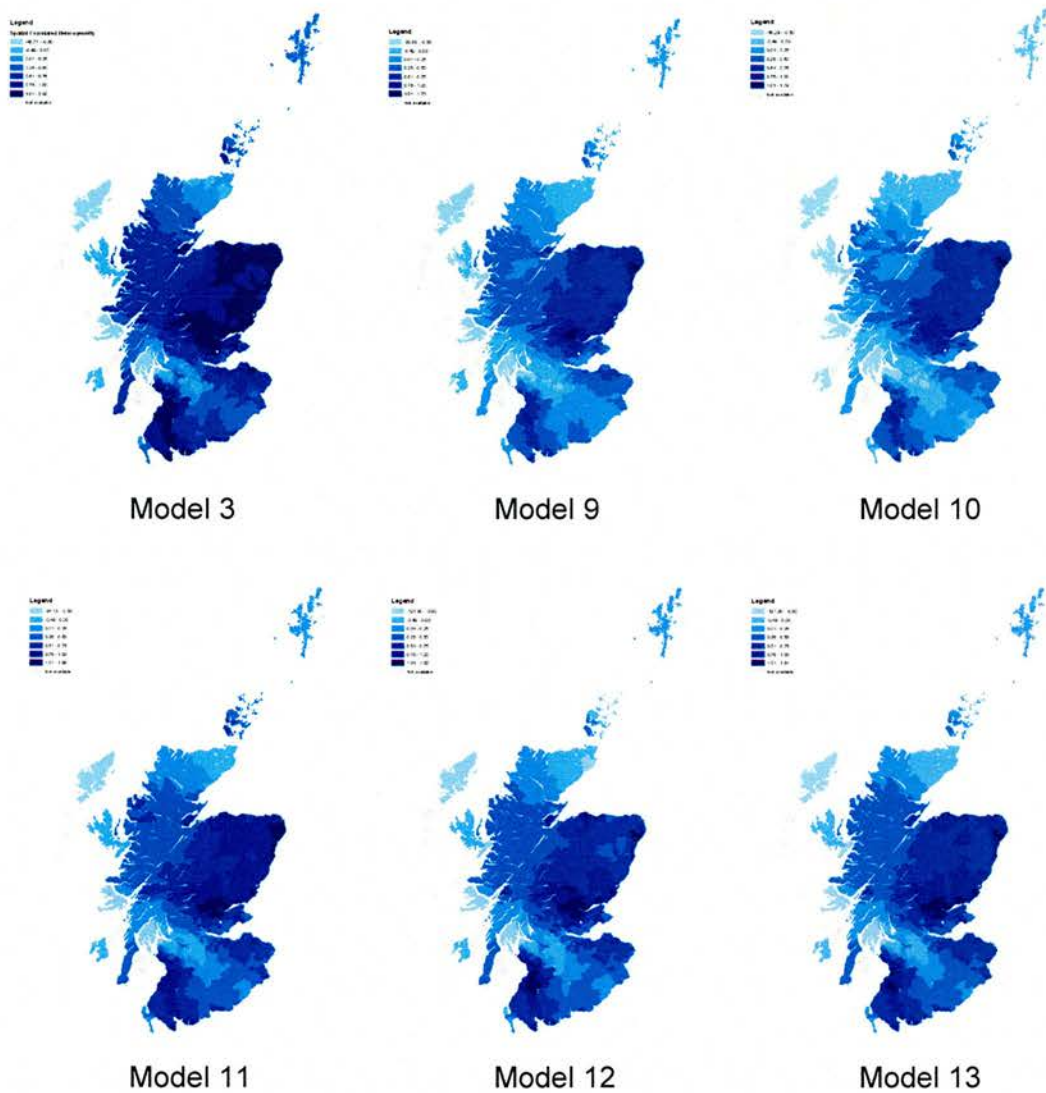
A similar conclusion can be made when comparing the spatial variation of the non-spatially correlated heterogeneity term produced by the BYM models; all are similar except for the BYM model with mean radon (Figure 121). However the BYM model without a covariate included and the BYM model plus mean radon also have a smaller range of values than the other models.

**Figure 121** Hypospadias posterior spatially uncorrelated heterogeneity term from BYM plus variable models



The spatial variation of the spatially correlated heterogeneity term produced by the BYM models show the same pattern as each other and as the estimates of the relative risks. However the model with no covariates shows the largest heterogeneity values. Therefore the inclusion of the other covariates might have explained some of the extra variation, even though this did not result in a reduction of the DIC values.

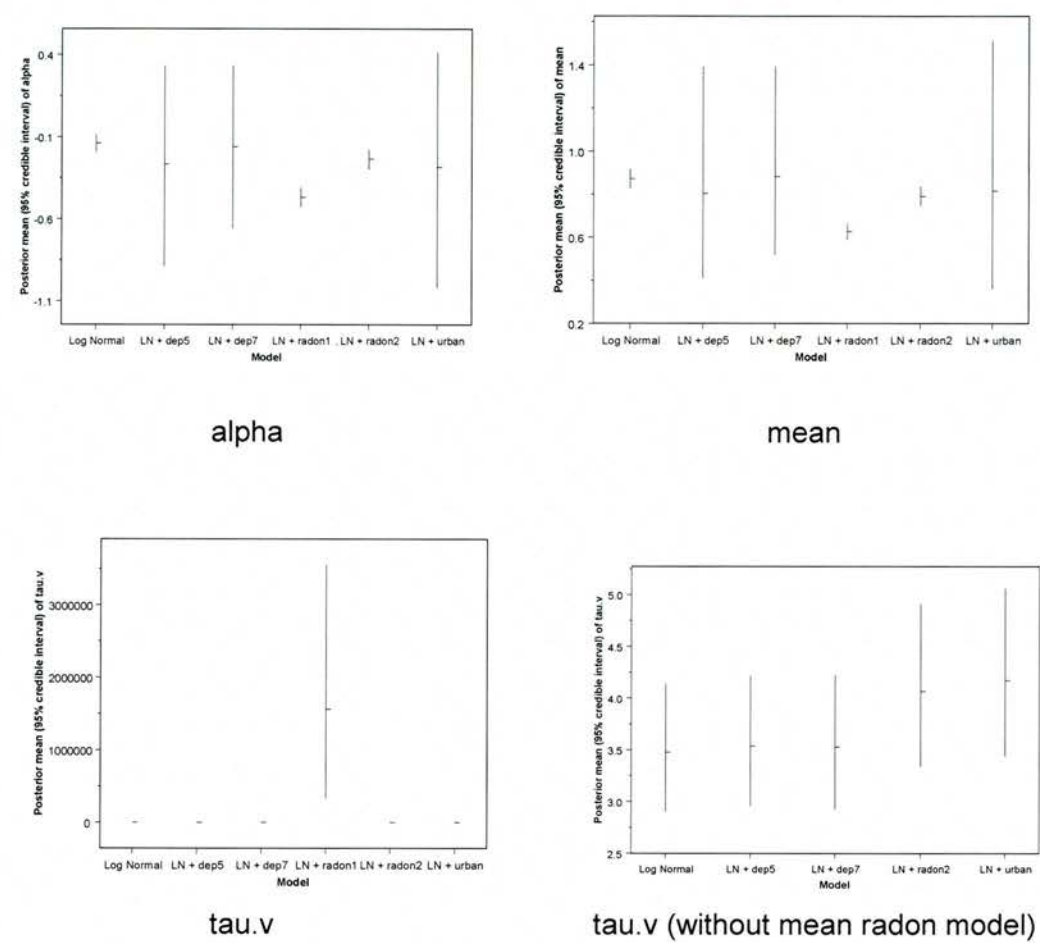
**Figure 122** Hypospadias posterior spatially correlated heterogeneity term from BYM plus variable models



Apart from the postcode specific posterior estimates produced by the models, there are model parameters that might provide more information on how successful the inclusion of potential covariates have been in explaining the spatial variation of the

hypospadias risk. Figure 123 shows the posterior estimates of the parameters for the different Log-Normal models.

**Figure 123** Posterior estimates for non postcode specific parameters in Log-Normal models



The mean intercept term ( $\alpha$ ) estimates are generally negative and similar although the wide credible intervals on a number of the models mean that it is unclear if all the estimates are negative. The largest negative value is for the Log-Normal plus mean radon model, which is the worse fitting model to the hypospadias data. In general then, the intercept is of a small negative value, which is largely unaltered by the inclusion of possible covariates except in the precision of its estimate.

The population mean relative risk (mean) estimates shows a similar pattern to the intercept estimates, in terms of changes made by the inclusion of the potential

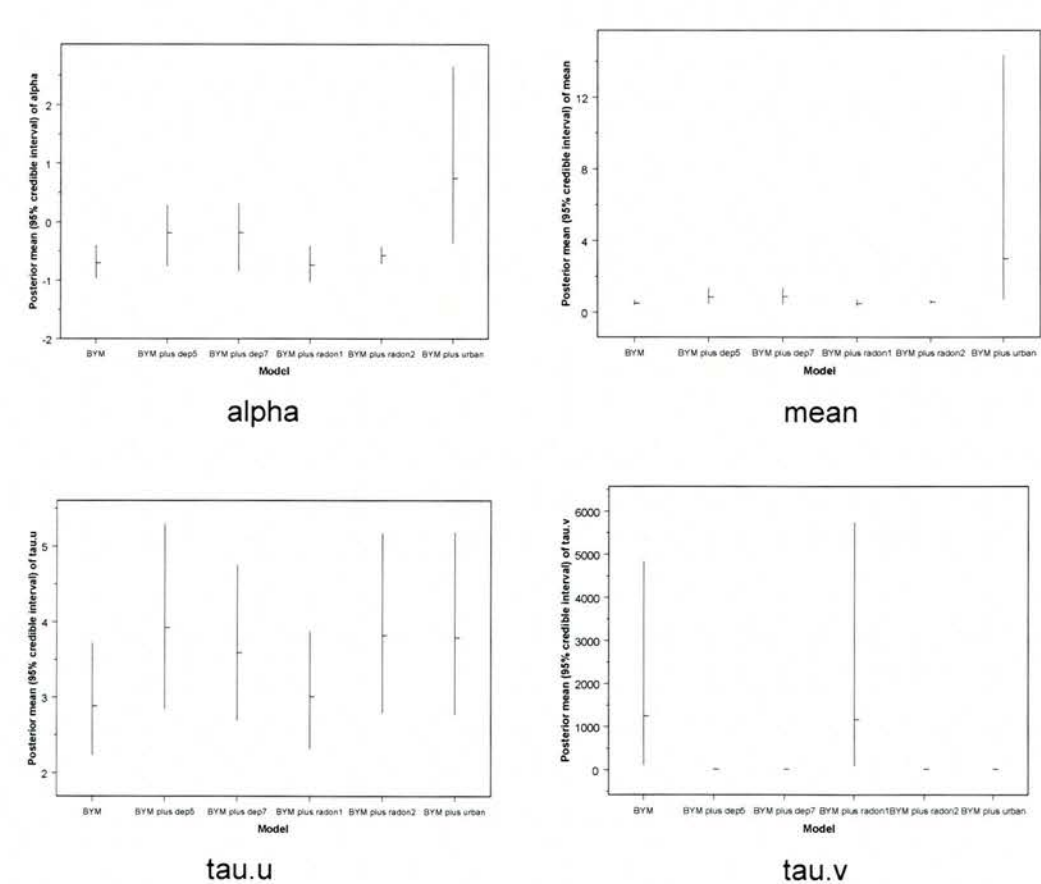


covariates. All estimates from the different models show a population relative risk of below 1 with different precisions of the estimate for different models. There are wider credible intervals on the deprivation and urban/rural indicator model. Again the lowest value is that produced by the Log-Normal plus mean radon model.

The precision of the non-spatially correlated heterogeneity term ( $\tau_{u,v}$ ) is similar in all the models except that with mean radon, where the precision is much poorer. This is consistent with previous assessments of this model. When looking at the precision of the non-spatially correlated heterogeneity term for the other models, the precision deteriorates slightly in those models that appear to improve the fit of the data compared to the basic Log-Normal model i.e. the urban/rural indicator and the percentage of a region that has radon measurements greater than 200 Bq/m<sup>3</sup> models.

Do any of these parameter estimates alter with the inclusion of the spatially correlated heterogeneity term? (Figure 124)

**Figure 124** Posterior estimates for non postcode specific parameters in BYM models



In general the model parameters are the same, although there are some changes. The mean intercept terms ( $\alpha$ ) remains below zero except for that for the BYM model with urban/rural indicator, which is now more likely to be positive. The population relative risk estimates remains below 1 except again for the urban/rural indicator model, which now shows an excess relative risk, all be it with wide credible intervals. The precision of the non-spatial heterogeneity term ( $\tau.v$ ) deteriorates with the inclusion of the spatially correlated term; however with the inclusion of most of the covariates (except radon) this is reversed. The estimates of the precision of the spatially correlated term ( $\tau.u$ ) are increased by the inclusion of any of the potential covariates worsens it.

### **6.7.2 Conclusions of Inclusion of Covariates**

While the DIC results from the Log-Normal model indicate that the percentage of a region that has radon measurements greater than 200 Bq/m<sup>3</sup> or the rural/urban indicator might explain some of the spatial variation, this is not confirmed from the BYM models results. However, from the comparison of the spatial variations of the relative risks and heterogeneity terms there appears to be a reduction in the variability of their values in both the Log-Normal and BYM models, when these covariates are included.

This discrepancy in the performance of the these two covariates in the BYM model could be due to the spatially correlated heterogeneity term soaking up any extra variation which we want to explain. For instance, the precision of the non-spatial heterogeneity term deteriorates with the inclusion of the spatially correlated heterogeneity term which is then reversed by the inclusion of most of the potential covariates.

Therefore there is some evidence to show that the spatial variation in the testicular cancer relative risks might be associated with the rural/urban indicator and the mean radon measurement of that postcode sector.

## 6.8 Summary of Hypospadias Analysis

There does appear to be spatial pattern to the hypospadias relative risks across Scotland. The relative risk estimates from each of the three Bayesian disease count models found clusters of high relative risks in the East and South-West of Scotland with lower risks in the region between the Central Borders and the West of Scotland.

In general the BYM model was the best fit to the hypospadias data although as with the other two condition/diseases suspicions are raised on the performance of the spatially correlated term used in the model. While the Poisson-Gamma and the Log-Normal model identified that the heterogeneity might be spatially correlated, it is not clear if the term used within the BYM model over-smoothes this heterogeneity.

There is some evidence to show that the percentage of a region that has radon measurements greater than 200 Bq/m<sup>3</sup> or the rural/urban indicator might explain the spatial variation of the hypospadias relative risks.



## **Chapter 7 : Combined analysis of male reproductive health conditions**

### **7.1 Introduction**

This chapter reports the results of the conjoint analysis of the three indicators of male reproductive health previously analysed separately: cryptorchidism, hypospadias and testicular cancer. The justification for this approach is detailed in 3.8 where the development of the multi-indicator model in WinBUGs is also described.

This chapter consists of three sections. Before detailing the results of the multi-indicator model the first section summarises the results of the individual indicators disease count models. The purpose of this section is to provide an initial comparison of the spatial variations of the three indicators. It is not to compare the performance of the Bayesian models with each of the disease/conditions data, as this been done in the individual disease/condition result chapters.

The second section details the results from the multi-indicator model in three parts:

- (i) 7.3.1 provides a comparison of the goodness of fit of the three multi-indicator models ran in WinBUGs, to show which heterogeneity terms best explain the joint spatial distribution of the indicators.
- (ii) 7.3.2 details and compares the posterior estimates of the area-specific estimates produced by the multi-indicator models, to show the spatial variation of the estimates of the relative risks.
- (iii) 7.3.3 assesses the relationships between the relative risks estimates of the three indicators produced by the three multi-indicator models, to show if spatial relationships exist between them and further asses the performance of the multi-indicator models.

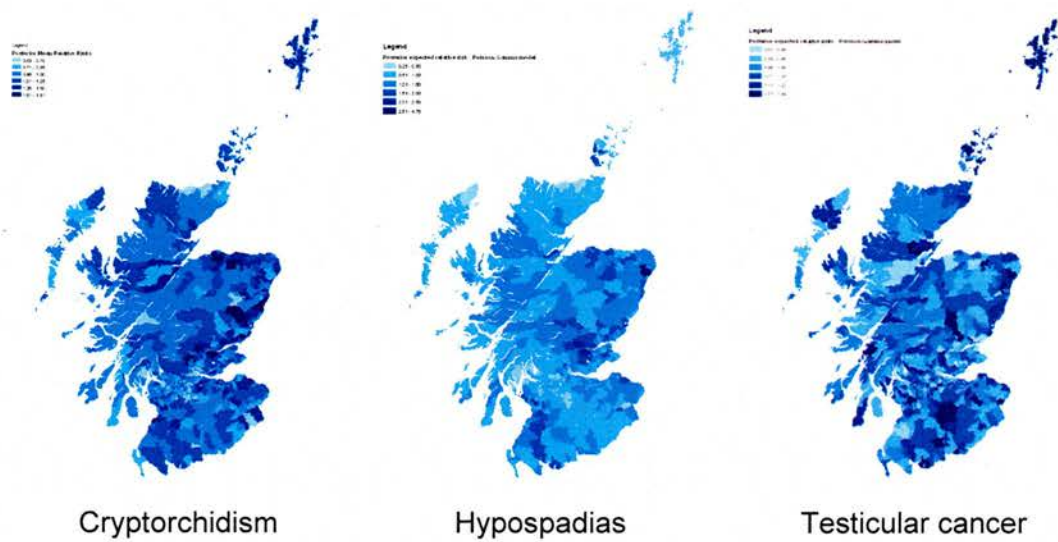
Finally, as with all the analysis chapters, the results of the multi-indicator analysis are summarised and points are highlighted for further discussion.

## 7.2 Comparison of individual Bayesian Hierarchical disease count models

The figures below show the relative risks estimated from the separate Bayesian Hierarchical disease count models for each indicator. The purpose of these maps is to compare the spatial variation in relative risks for the three indicators produced separately by the same model. Therefore we are comparing the variation in colour gradients rather than values, and so the cut-off values do not need to be, and are not, the same within each figure.

Comparing the relative risks estimates produced by the Poisson Gamma model separately for the three indicators, the spatial variation is similar in cryptorchidism and hypospadias (Figure 125). There are clusters of higher relative risks in the North East and South West with a corridor of lower relative risks from the central borders to the West coast. However the spatial pattern is more distinct for the hypospadias relative risks than cryptorchidism. There is not such a distinct spatial pattern to the testicular cancer relative risks, nor is it similar to those of the hypospadias and cryptorchidism estimates.

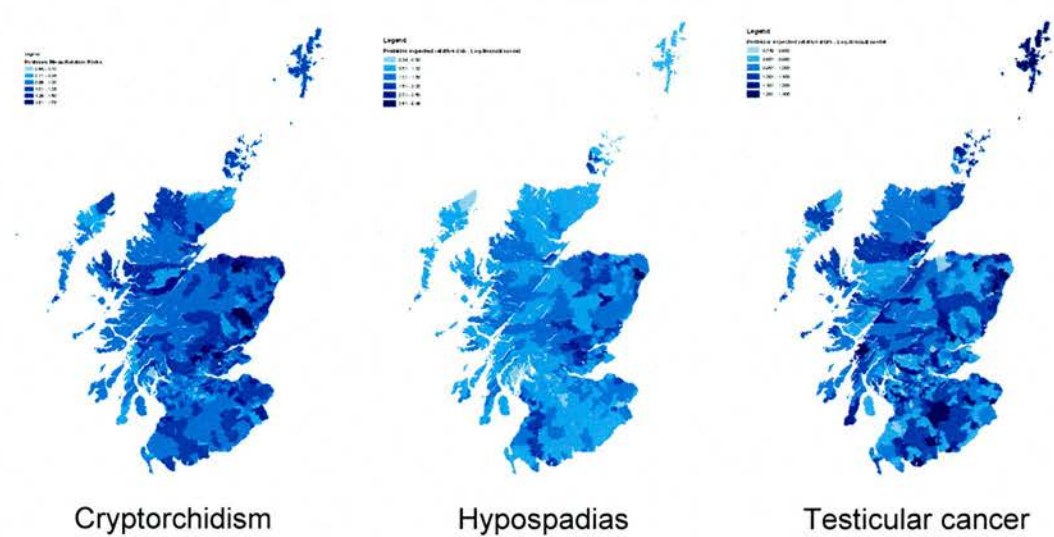
**Figure 125 Comparison of relative risks produced by the Poisson-Gamma model for the three indicators**



The similarities in spatial variation of the cryptorchidism and hypospadias estimates produced by the Poisson-Gamma model are also found in those estimated from the

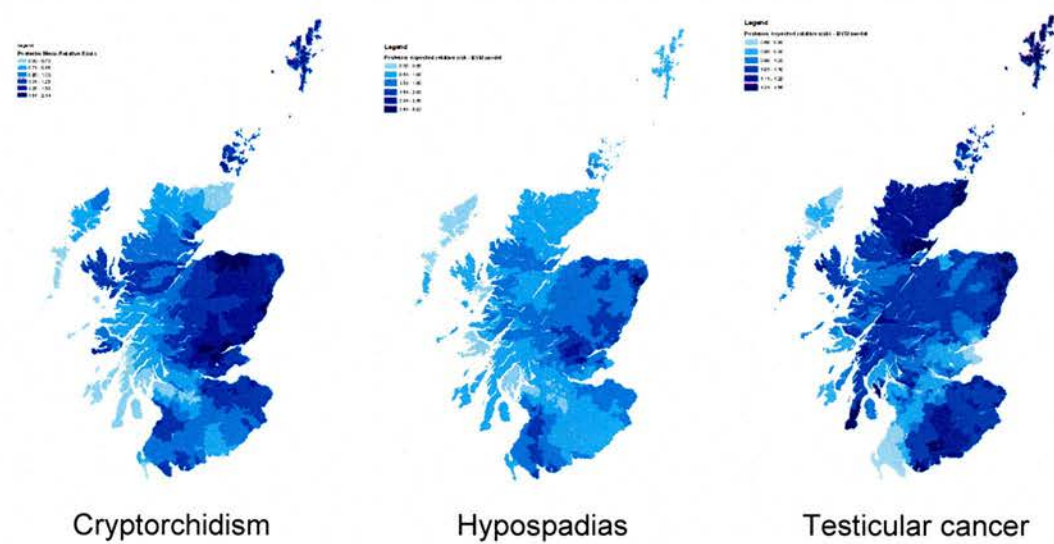
Log-Normal model (Figure 126). And, as in the Poisson-Gamma model, there does not appear to be a spatial pattern for the testicular cancer estimates that is similar to those produced for the cryptorchidism and hypospadias data.

**Figure 126 Comparison of relative risks produced by the Log-Normal model for the three indicators**



For all the indicators, the estimates produced by the BYM model have a much more pronounced spatial pattern (Figure 127).

**Figure 127 Comparison of relative risks produced by the BYM model for the three indicators**





Again, the hypospadias and cryptorchidism spatial patterns are similar to each other, although the patterns are much more distinct than in the other models' estimates. The testicular cancer spatial pattern produced by the relative risks from the BYM model is very different from that produced by the other two Bayesian models. There are similarities to the testicular cancer risk and the hypospadias and cryptorchidism spatial variation produced by the BYM model. There are higher relative risks in the north-east like cryptorchidism and hypospadias. However, testicular cancer appears to also have higher relative risks in the whole of the north and south and lower relative risks in the central belt.

Yet, as discussed in the individual indicators results chapters, there are suggestions that the spatially correlated heterogeneity term in the BYM model over-smoothes the heterogeneity. Therefore the spatial variation of the testicular cancer relative risks might not be as pronounced as those estimated by the BYM model.

Therefore, there are suggestions that there are similarities in the spatial variation of cryptorchidism and hypospadias when comparing the estimates produced from the separate models. However, it is unclear that the spatial variation of testicular cancer is similar to the other indicators.

## **7.3 Multi-indicator model results**

The previous section compares the spatial pattern of the relative risks estimated separately for the three indicators. However for reasons already outlined (section 3.8) a more elegant approach would be to model the three indicators conjointly.

### **7.3.1 Comparison of multi-indicator models**

As well as the multi-indicator model outlined in section 3.8, two other multi-indicator models were run in WinBUGs to ascertain which of the heterogeneity terms best explain the joint spatial distribution of the three indicators. Table 47 details the three models ran and the results of the DIC diagnostics. Comparing the DIC results for the models, the most successful fit of the data is that which includes both heterogeneity terms. Therefore the variation of the joint distribution of the three indicators would appear to have both a spatial and random component.

Table 47    DIC results of Multi-indicator models

Model	$\overline{D}$	$D(\overline{\mathcal{G}})$	pD	DIC
1. Multi-indicator model with both heterogeneity terms	9571	2587	6984	16555
2. Model 1 with only uncorrelated heterogeneity	9753	2769	6984	16737
3. Model 1 with only spatially correlated heterogeneity	9627	2643	6984	16611

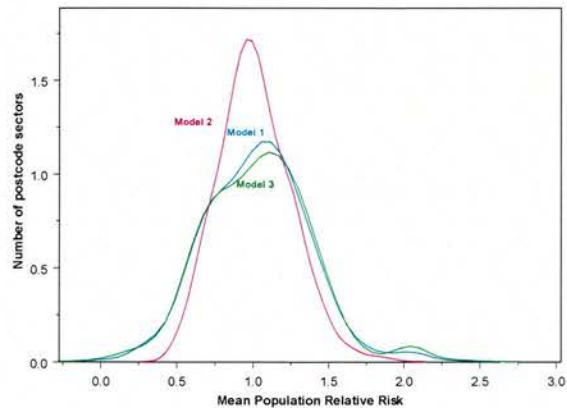
Moreover, the DIC for the model with only the spatially correlated heterogeneity (model 3) is lower than the model with only the uncorrelated heterogeneity (model 2). Therefore there is evidence to show that the variation of the joint distribution of the indicators has a stronger spatial component than a random one.

7.3.2 Area-specific posterior estimates of multi-indicator models

Figures 128-130 show the distributions of the relative risk estimated by the three multi-indicator models for the three indicators, to see how the inclusion of the heterogeneity terms alters the relative risk estimates. It is assumed a particular model is an improvement on another when the distribution of the relative risks is narrower, as it is indicating a reduction in the variability of the estimates.

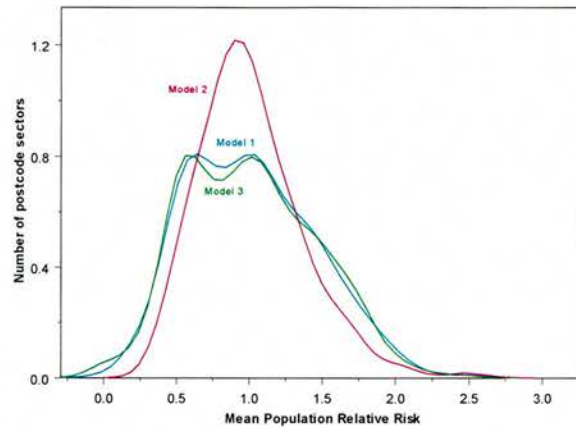
For all the conditions, to a lesser or greater extent, the distributions of the relative risk estimates are altered by the inclusion of the spatially correlated heterogeneity term. The narrowing of the distributions of the relative risks by the spatially correlated heterogeneity term can be seen most noticeably for cryptorchidism (Figure 128) and hypospadias (Figure 129).

Figure 128 Cryptorchidism multi-indicator models results: distribution of posterior estimates of relative risks per 1991 postcode sector



In both indicators model 2, which has only the non-spatially heterogeneity term, narrows the distribution of the relative risk estimates the greatest. Furthermore, model 1, which contains both heterogeneity terms, has produced a distribution very similar to that for model 3, which only has the spatially heterogeneity term.

**Figure 129 Hypospadias multi-indicator models results: distribution of posterior estimates of relative risks per 1991 postcode sector**

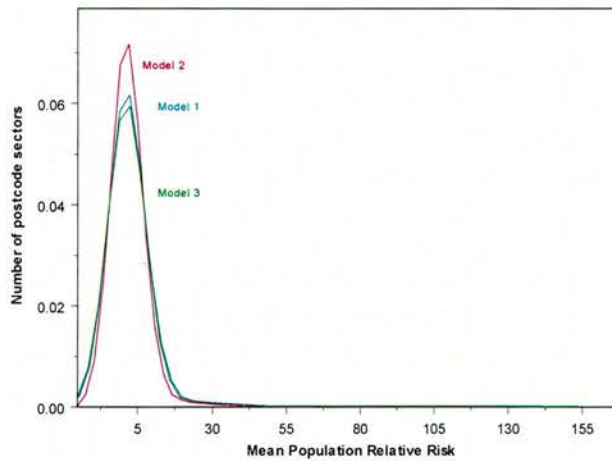


Therefore, for these two indicators, the non-spatially heterogeneity has little effect on the distribution of the relative risk estimates within the model with both heterogeneity terms, and removes more of the estimates' variability. This provides more evidence that the heterogeneity for these indicators is strongly spatially correlated.

The differences in the relative risks distributions between model 2 and models 1 and 3 found in the cryptorchidism and hypospadias datasets is not as distinct in the testicular cancer estimates (Figure 130). While the distribution of the relative risks produced by model 2 is narrower than that for the other two models, the difference is slight. Therefore the spatially correlated heterogeneity term does not impact on the relative risk estimates produced for the testicular cancer to as great extent as those for cryptorchidism and hypospadias. So it would appear that there is less of a spatial component to the variation of the testicular cancer relative risks.



**Figure 130 Testicular cancer multi-indicator models results: distribution of posterior estimates of relative risks per 1991 postcode sector**

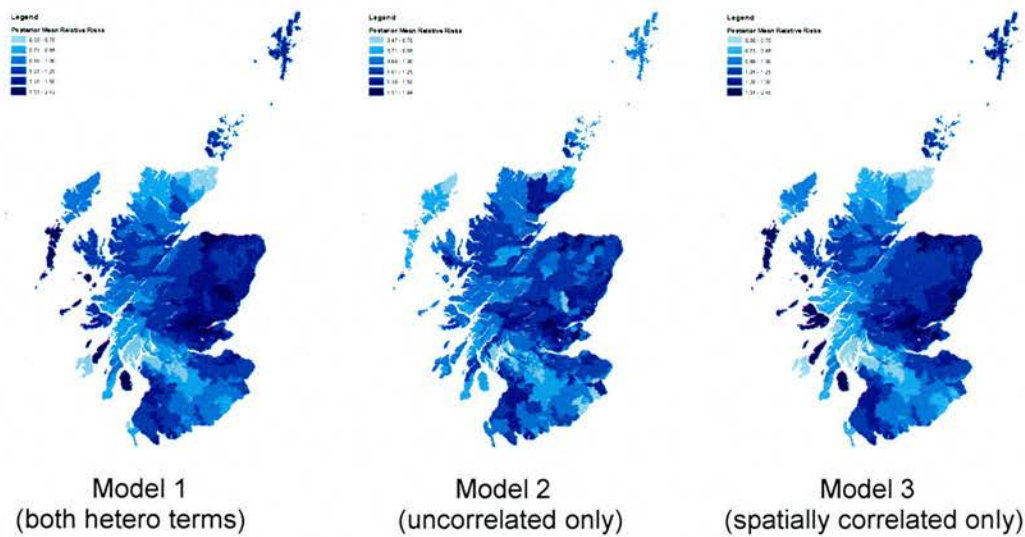


Do the differences in the distributions of the relative risks for the 3 indicators produced by the multi-indicator models alter the spatial variation of these indicators? A comparison of the spatial variation of the relative risks produced by the 3 multi-indicator models will give further insight into the performance of the heterogeneity terms on the three indicators. The next 3 figures show the spatial variation of the relative risks for the three indicators produced by the three multi-indicator models (Figures 131-3). The cut-offs used in each figure are those used for the equivalent disease in Figures 125 to 127, so that they are equivalent to those produced in the separate indicator models.

The spatial variations of the relative risks produced from the multi-indicator model for cryptorchidism are similar to those produced by the separate cryptorchidism disease count models (Figure 131 vs. cryptorchidism in Figures 126 and 127). Therefore the spatial variations of the estimates for the cryptorchidism relative risks have not been altered by being estimated from the multi-indicator model rather than the separate indicator models. As the spatial variation of the cryptorchidism relative risks produced by Model 1 and Model 3 (spatially correlated heterogeneity only) are very similar, it would appear that the uncorrelated heterogeneity term has little impact on the estimates when included with the spatially correlated heterogeneity. Furthermore, as the spatial variation of the cryptorchidism relative risks produced by Model 1 are much more distinct than those produced by Model 2 (uncorrelated

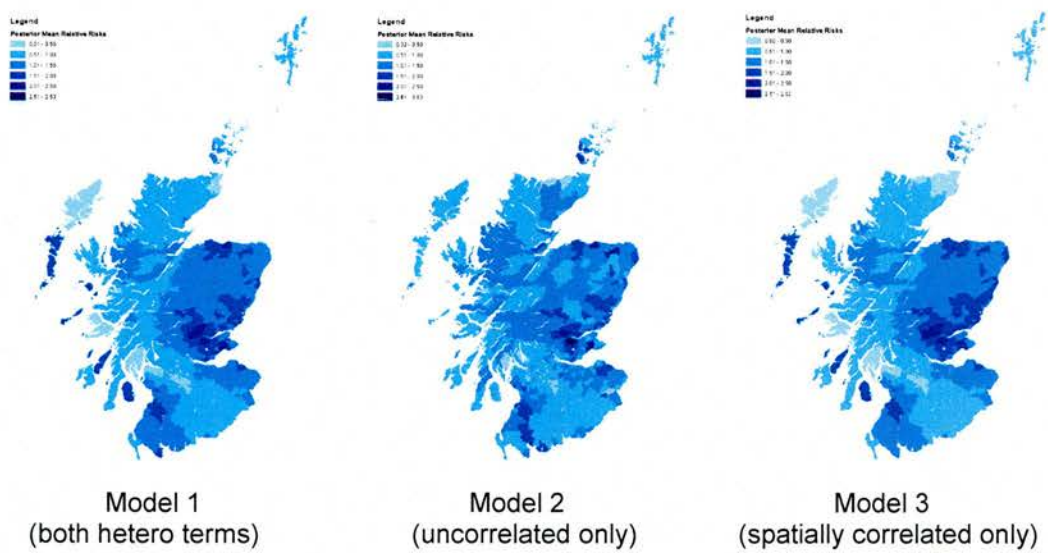
heterogeneity only), then the spatial correlated heterogeneity appears to have a greater role in smoothing the variability of the relative risk estimates for cryptorchidism.

**Figure 131 Cryptorchidism multi-indicator model results: posterior estimates of relative risks per 1991 postcode sector**



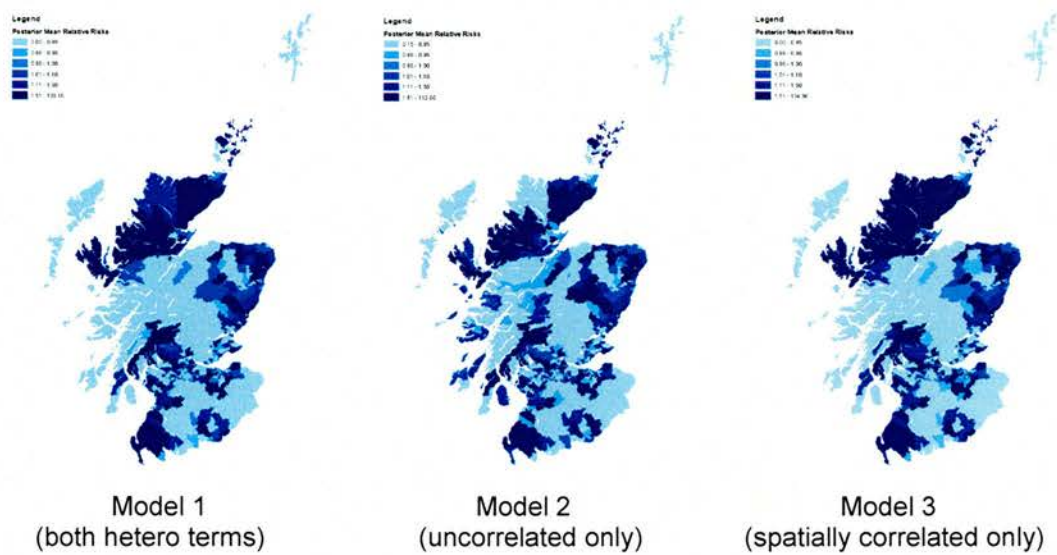
Similar comparisons and conclusions can be made between the spatial variations of the relative risks produced from the multi-indicator models for hypospadias (Figure 132).

**Figure 132 Hypospadias multi-indicator models results: posterior estimates of relative risks per 1991 postcode sector**



The spatial variations of the relative risk estimates for testicular cancer from the multi-indicator models are considerably different from those produced by the individual testicular cancer count models (Figure 133 vs. testicular cancer in Figures 126 and 127).

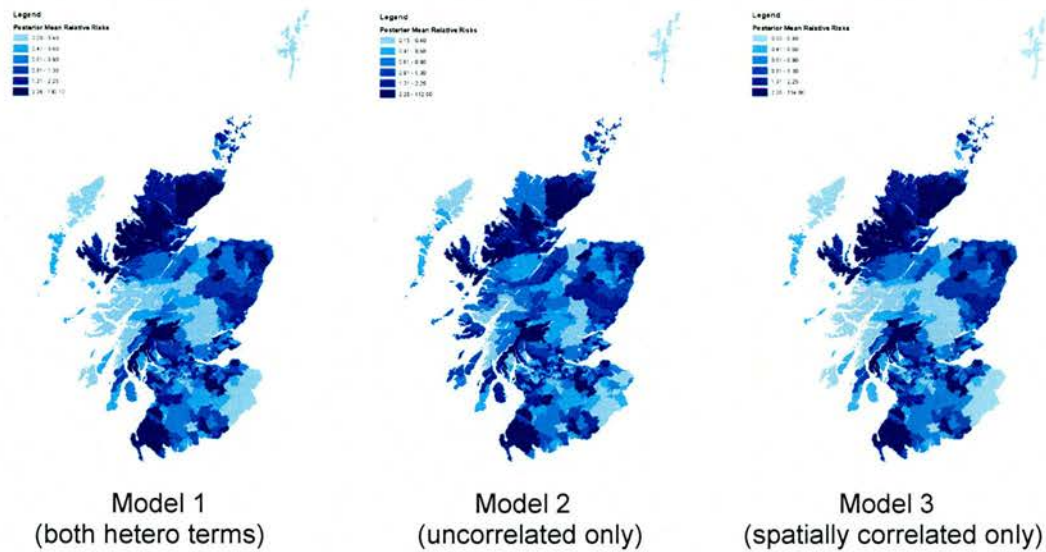
**Figure 133 Testicular cancer (comparison cut-offs) multi-indicator models results: posterior estimates of relative risks per 1991 postcode sector**



The spatial variations of the relative risk estimates from these three multi-indicator models for testicular cancer are very similar; which mirrors the comparison of the distributions of the estimates of the various multi-indicator models (Figure 130). The relative risk estimates produced by the multi-indicator models for testicular cancer are generally larger than those produced by the separate individual models. So it is likely that the multi-indicator models are not successful at modelling the testicular cancer relative risks compared to the cryptorchidism and hypospadias data.

In order to compare the spatial variation of the testicular cancer relative risks produced by the three multi-indicator models, the cut-off values need to be altered. Figure 134 shows the spatial variation of the three multi-indicator models with the altered cut-offs.

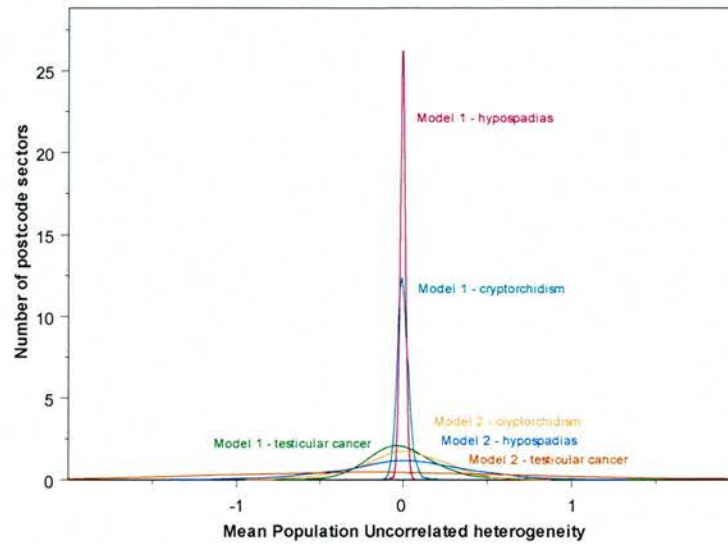


**Figure 134 Testicular Cancer multi-indicator models results: posterior estimates of relative risks per 1991 postcode sector**

As with cryptorchidism and hypospadias the spatial variation of the testicular cancer relative risks produced by Model 1 and Model 3 (spatially correlated heterogeneity only) are very similar. Therefore it would appear that the uncorrelated heterogeneity term has little impact on the estimates when included with the spatially correlated heterogeneity term. However, the spatial variation of the testicular cancer relative risks produced by Model 1 is similar to those produced by Model 2 (uncorrelated heterogeneity only). So the spatially correlated heterogeneity does not appear to have as strong effect on smoothing the variability of the relative risk estimates for testicular cancer, as compared to cryptorchidism and hypospadias.

To further examine the effect of the heterogeneity terms on the overall performance of the multi-indicator model, we can examine the estimates of the heterogeneity estimated by the three multi-indicator models. Figure 135 shows the distribution of the uncorrelated heterogeneity produced for the three indicators from the three multi-indicator models, while Figure 136 shows the distributions for the spatially correlated heterogeneity.

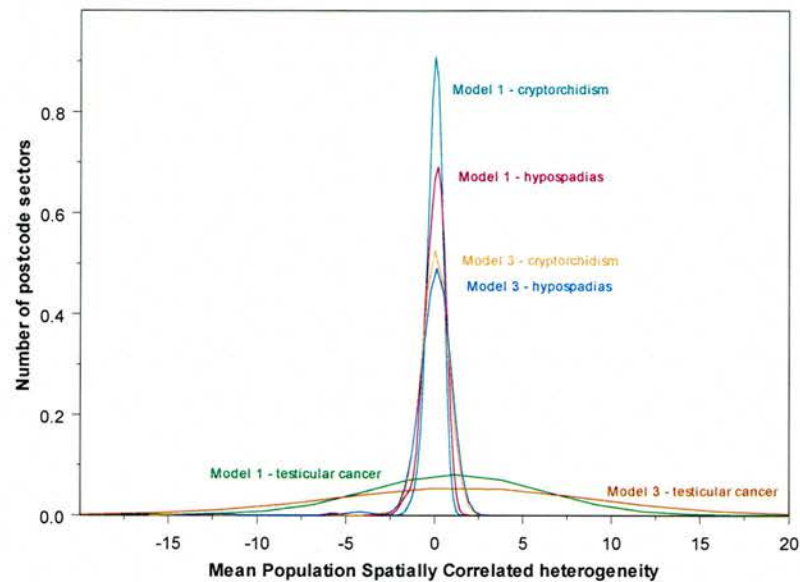
**Figure 135 Distribution of Posterior estimates of uncorrelated heterogeneity per 1991 postcode sector from multi-indicator models**



From Figure 135, irrespective of indicator, the uncorrelated heterogeneity is narrowed for the model with both heterogeneity terms compared to that with only random heterogeneity. Therefore the variability of the random heterogeneity is reduced by the inclusion of the spatially correlated heterogeneity and so the inclusion of both heterogeneity terms reduced the uncorrelated unexplained variation of the joint distribution of these indicators. Furthermore, the distributions of the hypospadias and cryptorchidism uncorrelated heterogeneity are narrower than those for testicular cancer, irrespective of model. Therefore these two indicators are modelled better in the multi-indicator model than the testicular cancer data.

The same conclusions can be made from the comparisons of the estimates of the spatially correlated heterogeneity from the multi-indicator models (Figure 136). However, the differences in the models with both heterogeneity terms compared to those with only the spatially correlated heterogeneity is not as great as seen for the uncorrelated heterogeneity distributions. Therefore, this would imply that the spatially correlated heterogeneity is a stronger component of the multi-indicator model, than the uncorrelated heterogeneity.

**Figure 136** Distribution of Posterior estimates of spatially correlated heterogeneity per 1991 postcode sector from multi-indicator models



### 7.3.3 Spatial Relationships between disease/conditions

Assessed visually there do appear to be similarities between the spatial variation of the relative risks of cryptorchidism and hypospadias, and little between them and testicular cancer. These possible correlations can be tested formally by comparing particular terms specified in the multi-indicator model. Table 48 summarises the parameters that are compared across the three multi-indicator models which have been detailed further in section 3.8. Table 49 shows the posterior means (and 95% credible intervals) for these parameters produced by the three multi-indicator models.



**Table 48** Descriptions of parameters included in multi-indicator models

Parameter	Description of parameter
a[1]	Intercept term for Cryptorchidism model
a[2]	Intercept term for Hypospadias model
a[3]	Intercept term for Testicular Cancer model
corr.sum1	Within-area correlation between total heterogeneity of Cryptorchidism and Hypospadias
corr1	Within-area correlation between spatial heterogeneity of Cryptorchidism and Hypospadias
corr1.v	Within-area correlation between random heterogeneity of Cryptorchidism and Hypospadias
corr.sum2	Within-area correlation between total heterogeneity of Cryptorchidism and Testicular Cancer
corr2.u	Within-area correlation between spatial heterogeneity of Cryptorchidism and Testicular Cancer
corr2.v	Within-area correlation between random heterogeneity of Cryptorchidism and Testicular Cancer
corr.sum3	Within-area correlation between total heterogeneity of Hypospadias and Testicular Cancer
corr3.u	Within-area correlation between spatial heterogeneity of Hypospadias and Testicular Cancer
corr3.v	Within-area correlation between random heterogeneity of Hypospadias and Testicular Cancer
sigma.u[1]	Standard Deviation of spatial heterogeneity of Cryptorchidism
sigma.u[2]	Standard Deviation of spatial heterogeneity of Hypospadias
sigma.u[3]	Standard Deviation of spatial heterogeneity of Testicular Cancer
sigma.v[1]	Standard Deviation of random heterogeneity for Cryptorchidism
sigma.v[2]	Standard Deviation of random heterogeneity for Hypospadias
sigma.v[3]	Standard Deviation of random heterogeneity for Testicular Cancer

**Table 49** Parameter estimates from multi-indicator models

Means (95% credible intervals) for parameters					
Parameter	Model 1		Model 2		Model 3
	Both heterogeneity terms		Model 1 without spatially correlated heterogeneity		Model 1 without uncorrelated heterogeneity
a[1]	-0.08	(-0.14, -0.03)	-0.04	(-0.09, 0.01)	-0.08 (-0.13, -0.02)
a[2]	-0.16	(-0.21, -0.12)	-0.11	(-0.17, -0.06)	-0.22 (-0.28, -0.16)
a[3]	-1.72	(-2.44, -0.72)	-0.11	(-0.20, -0.02)	-1.71 (-2.09, -1.22)
corr.sum1	0.89	(0.78, 0.97)	0.97	(0.89, 0.99)	0.96 (0.88, 1.00)
corr1.u	0.97	(0.91, 0.99)	-		0.94 (0.85, 0.99)
corr1.v	-0.34	(-0.86, 0.45)	0.96	(0.89, 0.99)	-
corr.sum2	0.15	(-0.10, 0.38)	0.25	(0.01, 0.40)	0.19 (-0.04, 0.49)
corr2.u	0.11	(-0.14, 0.35)	-		0.26 (-0.01, 0.53)
corr2.v	0.71	(-0.18, 0.96)	0.26	(0.05, 0.47)	-
corr.sum3	0.09	(-0.11, 0.32)	0.18	(0.05, 0.32)	0.07 (-0.13, 0.27)
corr3.u	0.12	(-0.09, 0.34)	-		0.06 (-0.12, 0.25)
corr3.v	-0.38	(-0.84, 0.59)	0.18	(0.04, 0.31)	-
sigma[1]	0.34	(0.29, 0.38)	-		0.35 (0.27, 0.42)
sigma[2]	0.48	(0.43, 0.56)	-		0.49 (0.43, 0.55)
sigma[3]	1.55	(1.35, 1.76)	-		1.82 (1.68, 1.96)
sigma.v[1]	0.10	(0.05, 0.16)	0.34	(0.29, 0.40)	-
sigma.v[2]	0.07	(0.04, 0.13)	0.50	(0.46, 0.55)	-
sigma.v[3]	0.45	(0.31, 0.58)	1.16	(1.08, 1.23)	-

Irrespective of multi-indicator model, there is evidence to suggest a strong shared geographical pattern of risk between cryptorchidism and hypospadias. Firstly, there is a high correlation between the spatially structured risk components for cryptorchidism and hypospadias (Model 1 – 0.97; 95% CI: 0.91, 0.99). Furthermore, as the spatial component dominates, the correlation between the total random effect is also high (Model 1 – 0.89; 95% CI: 0.78, 0.97). Therefore, there does appear to be a shared geographical pattern of risk between cryptorchidism and hypospadias, furthermore there is to a lesser extent a spatially uncorrelated risk between the two diseases. So there would appear to be spatially varying factor(s) associated with the two conditions, and some evidence that non-geographically varying risk factor(s) are also associated with cryptorchidism and hypospadias although to a lesser extent.

However, there is evidence that the spatially correlated heterogeneity over-smoothes the spatially structured component. When comparing the estimates of the parameters estimated from the three models, most are considerably altered by the removal of the spatially correlated heterogeneity term (Model 2 v Model 1). This alteration in the parameters estimates does not occur to the same degree when the spatially uncorrelated heterogeneity term is removed. For example, the small statistically non-significant correlation between the spatially uncorrelated risk of cryptorchidism and hypospadias ( $\text{corr1.v}$ ) estimated from model 1 (-0.34; 95% CI: -0.86, 0.45), becomes a strong statistically significant correlation estimated from model 2 (0.96; 95% CI: 0.89, 0.99). As the change in the terms included in these models is the removal of the spatially correlated heterogeneity, then it would appear that this term has a considerable effect on the multi-indicator model.

None of the other possible combinations of diseases show a correlation, so providing further evidence that testicular cancer does not have the same spatial variation as cryptorchidism and hypospadias. Furthermore, the standard deviations of the spatially correlated and uncorrelated random heterogeneities ( $\text{sigma.u}[3]$  and  $\text{sigma.v}[3]$  respectively) are the largest for testicular cancer irrespective of model, which provides evidence that the relative risk estimates for testicular cancer from the multi-indicator models are highly variable. Therefore the multi-indicator model does



not appear to successfully fit the testicular cancer data as well as the cryptorchidism and hypospadias data.

However, this can be tested by comparing the conditional likelihoods estimated within each multi-indicator model for each disease/condition. Table 50 shows the conditional likelihood estimates for each disease/condition within each multi-indicator. These were estimated in order to calculate the DIC results for each model and will show how well each disease/condition data fit the three multi-indicator models.

**Table 50** Conditional log likelihoods for each disease by multi-indicator model

Disease	Conditional log likelihoods (95% credible intervals)			
	Model 1 Both heterogeneity terms	Model 2 Model 1 without spatially correlated heterogeneity	Model 3 Model 1 without uncorrelated heterogeneity	
Cryptorchidism	871.8 (832.0, 910.4)	919.6 (863.3, 968.9)	891.8 (865.4, 917.8)	
Hypospadias	845.4 (800.2, 895.5)	906.6 (833.9, 981.5)	859.1 (808.7, 913.0)	
Test Cancer	870.1 (791.4, 954.3)	942.9 (859.8, 1,031.0)	891.8 (811.5, 973.8)	

In each multi-indicator model, the hypospadias data is the most successful fit. The testicular cancer data is the least successful fit in all three models; however in two of the three models (Models 1 and 3) there is no difference between it and the cryptorchidism data. Therefore, while the testicular cancer data is the least successful fit to the multi-indicator models, there is little difference in its success and that of the cryptorchidism data, contrary to what has been shown previously. However, it is interesting to note that for the least successful model (model 2), according to the DIC results seen in Table 50, the testicular cancer data is considerably the least successful fit. As this model does not contain the spatially correlated heterogeneity term it provides evidence that the variation of the joint distribution of the indicators has a stronger spatial component than a random one. Therefore as the testicular cancer data is the least successful fit to this model then the unexplained risk of this disease does not appear to be spatially correlated.

Finally, the standard deviations ( $\sigma_u$ ) of the random heterogeneities for the three indicators are greatly increased when the spatially correlated heterogeneity is removed from the multi-indicator model (Model 1 v Model 2). Therefore the



variability of the unexplained variation that is not spatially structured is greatly increased when both heterogeneity terms are not included in the model. So to decrease the variability of the estimates of the random heterogeneity the multi-indicator model with both heterogeneity terms should be used.

## **7.4 Summary of Multi-Indicator analysis**

From the conjoint analysis of the three indicators of male reproductive health there would appear to be a shared geographical pattern of risk between cryptorchidism and hypospadias, but not between them and testicular cancer.

Firstly the comparison of the relative risks estimated from the separate Bayesian Hierarchical disease count models showed a similarity in the spatial pattern between cryptorchidism and hypospadias. While the testicular cancer relative risks estimated from both the Poisson-Gamma and Log-Normal models did not produce similar spatial patterns to those produced for cryptorchidism and hypospadias, there were similarities for those relative risks produced by the BYM model. Although it must be noted that there are suspicions that the BYM model over-smoothes the spatial variation of this disease, based on the difference between the spatial variation of the estimates produced by the Log-Normal and BYM model.

The similarities in spatial pattern of the relative risks of cryptorchidism and hypospadias were shown again by the estimates of the relative risks and the correlations produced by the multi-indicator model. Furthermore, it was shown that the spatial pattern of the testicular cancer relative risks was not similar to cryptorchidism and hypospadias, and that the multi-indicator model was an unsuccessful fit for this disease.

The testicular cancer data would appear to be a poor fit to the multi-indicator model as the relative risks estimated were considerably different from those produced by the separate testicular cancer Bayesian models, the higher variability of the estimates produced and from the comparison of the conditional likelihoods. This poor performance was probably due to the testicular cancer data not following the assumptions outlined to be behind the multi-indicator model. It is assumed that in order for the model to produce smoother relative risks for a particular indicator it

‘borrows strength’ from the other indicators. For this to apply the spatial pattern of the relative risks of the indicators must be similar. While this appears to apply for cryptorchidism and hypospadias, it is not the case for testicular cancer. Therefore it is likely that the inclusion of the testicular cancer data would not be successful in the multi-indicator model.

So the multi-indicator model used here could have been developed further by reducing it to a two indicator model, including only cryptorchidism and hypospadias data. However, this was not carried out as this would not have altered the conclusion already found that these two conditions appear to share geographical pattern of risk. Where the two-indicator model would have been useful would have been to explore which of the potential covariates could explain the shared geographically varying risk. However, as this time it is not possible in WinBUGs to include further covariates when using the multivariate CAR distribution.

The strong association between the spatial pattern of the cryptorchidism and hypospadias relative risks does provide some evidence of a common aetiology. It shows that risk factor(s) that are geographically varying are associated with these two conditions. However, these spatially-varying risk factors are not necessarily environmental.

The differences in spatial variation of the testicular cancer relative risks compared to cryptorchidism and hypospadias could reflect both the known aetiology and the nature of the geographical data used for testicular cancer. For instance, testicular cancer incidence mainly occurs decades later than that of cryptorchidism and hypospadias, which are largely identified at birth. Furthermore, the data used for the three indicators reflect this difference as the location of each case is based on incidence. Therefore, the testicular cancer cases will reflect all potential exposure mechanisms rather than those only occurring *in utero* which would apply to the cryptorchidism and hypospadias data.

These conclusions from the combined analysis of the male reproductive conditions are considered further in the subsequent final discussion chapter.



## Chapter 8 : Discussion

This final chapter will bring together the thesis, by:

- interpreting the results from the analysis in terms of current research,
- discussing the strengths and weaknesses of the research carried out, and
- suggesting further work that stems from this research project.

### 8.1 Conclusions of spatial analysis

This section will review the results of the spatial analysis for each of the three disease/conditions and discuss them in relation to current male reproductive health research. From the spatial analysis carried out on each disease/conditions, only the relative risks estimated from the BYM model are discussed, as this model was the most successful fit for each disease/condition. The relative risks estimated from the conjoint analysis of the three disease/conditions are then compared to those from the BYM model. This comparison will determine if the conclusions made from the individual disease/conditions analysis are altered by the conjoint analysis results, while exploring the spatial relationships between the disease/conditions.

#### 8.1.1 Cryptorchidism

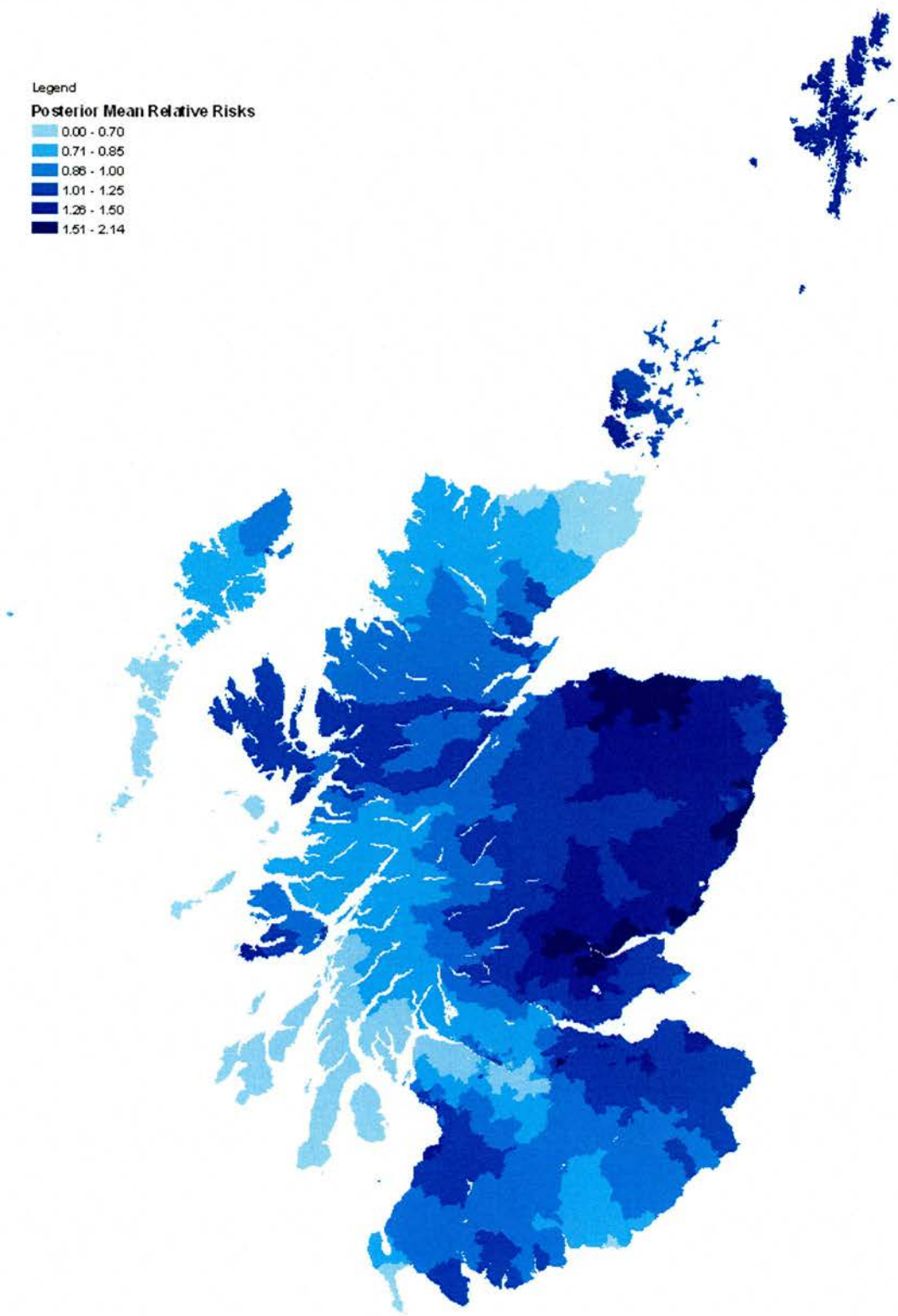
To review the spatial analysis, there does appear to be a distinct spatial pattern to the relative risks of cryptorchidism across Scotland (Figure 137):

- the East and South-West areas of Scotland have higher relative risks of cryptorchidism, while
- the North and the corridor from the central Borders to the West Coast are areas with lower relative risks.

The following area-specific covariates were found to explain the spatial variation of cryptorchidism: a rural/urban indicator (population density) and both radon measurements – i.e. mean radon level  $\text{Bq/m}^3$  within each postcode area and the proportion of measurements within a postcode area that exceeds  $200 \text{ Bq/m}^3$ . The spatial variation of cryptorchidism could also be explained by information concerning the cases themselves; namely maternal age and co-morbidity with hypospadias.



**Figure 137** Cryptorchidism posterior mean relative risks from BYM model: Scotland (1980-95) by 1991 postcode sector



Previous analysis of cryptorchidism has been criticised due to the use of inconsistent data (Toppari, Kaleva, and Virtanen, 2001). The reported increases in incidence and differences across geography were used to argue that an environmental risk factor was associated with cryptorchidism (Paulozzi, 1999). However this conclusion could be erroneous due to the inconsistencies in the data both across countries/registries and time. This research project's use of consistently collected data both over time and across the study region means that this potential bias is reduced, and we can see if the differences in time and geography still exist.

While the principle analysis of this project was spatial, a precursory analysis of the temporal trend of the incidence of cryptorchidism was carried out. In Scotland there would appear to be an increase in time of the incidence at birth of cryptorchidism (Figure 25), which mirrors previous results of UK data (Scorer, 1964; Ansell *et al.*, 1992). The number of cryptorchidism cases at birth in Scotland has risen by 36.8% over 15 years, from 4.08 cases per 1,000 births in 1980 to 5.58 cases per 1,000 births in 1995.

This increase in incidence could be due to exposure to increasing levels of an environmental factor. However, while it is unlikely that this temporal increase is due to changes in ascertainment, other factors could account for this trend. For instance, changes in the trends of maternal obesity, lower birth weight, preterm deliveries and the presence of other congenital malformations, could be involved and all have been found to be risk factors of cryptorchidism (Berkowitz *et al.*, 1995; Berkowitz and Lapinski, 1996). Furthermore, as older women might have a higher risk of congenital malformations and there is a trend to women having children when older, this might explain the increase in incidence (Baldwin and Nord, 1984). To further explore this, the spatial models could have been developed into spatial-temporal models.

Therefore, while the temporal trends in the incidence of cryptorchidism at birth signify that the underlying risk factors are also changing with time; it does not necessarily suggest that these are environmental risk factors. The aim of this research project was to examine the geographical variations of the incidence of cryptorchidism. It is assumed that if there is a geographical pattern to the risk of cryptorchidism then there is geographical-varying risk factor(s) associated with those



risks. Furthermore the identification of potential risk factors would highlight if the underlying risk is explained by environmental exposures and/or due to other geographically-varying risk factors.

As the relative risks of cryptorchidism have a distinct spatial pattern it would appear that the risk of cryptorchidism is associated with geographically-varying risk factor(s) (Figure 137). Furthermore, as cryptorchidism is identified at birth then there does appear to be evidence that the condition has geographically-varying foetal-origin aetiology (Kolon, 2002). Therefore the spatial variation of cryptorchidism risk provides some evidence to support the TDS hypothesis, namely that a geographically-varying factor for which exposure occurs *in utero* is associated with the condition. However as just highlighted, this possible aetiology does not necessarily have to be an environmental exposure. The assessment of the spatial pattern of the risk of cryptorchidism and those covariates found to be associated with it might highlight the nature of the underlying risk factors.

As can be seen in Figure 137, the higher relative risks in the East and South-West in Scotland are mainly rural areas. Furthermore, the rural/urban indicator used in the research project did explain some of the spatial variation of cryptorchidism, when included to the Bayesian disease count models. Therefore there would appear to be some rural/urban differences in the cryptorchidism risk in Scotland. One reason that these rural areas could have higher risks is that they might be farming areas. These areas might have a high use of pesticides, of which particular types are believed to have oestrogenic and/or anti-androgenic properties. Previous work has shown an association between semen quality and pesticide exposure (Jensen *et al.*, 1996).

However not all rural areas in Scotland appear to have high relative risks i.e. central Borders, West and far North, so it is likely that this possible exposure is not uniform across all rural areas (Figure 137). The non uniformity of the possible exposure could be due to the different types of rural areas in Scotland, e.g. farming and non-farming or different types of farming using different types and levels of pesticides. Therefore, to look at the role of farming and so pesticide use in more detail, it would be appropriate to use geo-referenced data on the different types of rural areas in Scotland and pesticide use.



The covariate used as the rural/urban indicator in this project was based on population density and so did not give any detail of the type of rural areas. Furthermore, this proxy measure may well encapsulate other rural/urban differences such as types of deprivation, diet and occupation. As seen in the review of the epidemiology of cryptorchidism and the other anomalies of male reproductive health these factors might also be associated with this condition (Berkowitz *et al.*, 1995; Berkowitz and Lapinski, 1996; Moller and Skakkebaek, 1996). Therefore, while there is an indication that there are rural/urban differences in the cryptorchidism risk in Scotland and the possible aetiology might be related to farming, the other differences between rural/urban areas might also explain the differences.

Both radon measurements also appeared to explain the spatial variation of cryptorchidism when included to the Bayesian disease count models. Radon exposure during pregnancy might result in damage to the foetus; whether directly to the boy's reproductive system or resulting in a genetic defect that results in a susceptibility to environmental chemicals. Although radon levels vary from home to home, the largest source of radon is geological; and the North-East of Scotland is the one region in Scotland with high levels of naturally occurring radon (NRPB, 2003). This is one of the areas with high relative risks of cryptorchidism and so radon might be associated with cryptorchidism risk. However, the inclusion of radon measurements into the Bayesian disease models might have been a success due to this strong correlation in values in one region of Scotland, rather than a 'true' association. This does not only apply to the inclusion of radon but the other covariates and is a disadvantage of ecological studies i.e. the spatial variation of a potential covariate might mirror the spatial variation of disease risk but not explain its aetiology. The potential of ecological bias was discussed in the methods chapter (3.3.4) and as will be seen shortly this potential bias was explored in relation to the cryptorchidism data.

Furthermore, there might be confounding between the rural/urban indicator and radon that could have resulted in all three variables being associated with cryptorchidism risk. Those regions that show high levels of radon are on the whole rural areas and vice-versa, and so there is an apparent association between these

covariates. Further development of the spatial models as outlined in 8.3.1.4 could explore this further.

The spatial pattern of the relative risks of cryptorchidism might also indicate genetic differences. It has been hypothesised that the decline in male reproductive health is due to the impact of both genetic susceptibility and exposure to environmental factors (Skakkebaek, Rajpert-De Meyts, and Main, 2001). And so the spatial differences in the cryptorchidism risk might reflect underlying genetic susceptibility. For instance, the impact of Nordic and Celtic settlements in Scotland could reflect the geographical variation of cryptorchidism and so particular ‘ethnic groups’ might have a different genetic susceptibility to the impact *in utero* of environmental chemicals. In broad terms, Nordic settlements were mainly in the East and North, while Celtic settlements were in the West. However, migration patterns both within and outwith Scotland will have diluted these settlement patterns. Furthermore, any genetic differences would be better explored and assessed by other types of studies.

While the assessment of the spatial variation of the risk of cryptorchidism and the area-specific covariates has highlighted potential aetiology, the individual analysis of the cryptorchidism cases can give further insights into the possible risk factors of this condition. The spatial variation of the maternal age is similar to the cryptorchidism relative risks in the North-East and North-West, but not in the South. For those in the North-East and North-West, those with older mothers have a higher risk of cryptorchidism. This reflects previous research that has found older women might have a higher risk of having children with congenital malformations (Baldwin and Nord, 1984). The association would only appear to apply to the spatial variation of cryptorchidism in the North-East and North-West of Scotland, and not to the south of Scotland. So it would appear that the cryptorchidism cases in the South have a different aetiology than those in the North and so different risk factors are associated with the variation in cryptorchidism risk in this region. Therefore, it is likely that within Scotland various risk factors will be associated with the spatial variation of cryptorchidism risk and which ones will be important will differ between regions of Scotland.



The spatial variation of the risk of the cryptorchidism cases also being diagnosed with hypospadias has similarities to that of the cryptorchidism risk in Scotland. Therefore, this similarity in the spatial variation of the co-morbidity of these two conditions does indicate some common aetiology that is geographically varying. This would correspond with the hypothesis that these and other anomalies of male reproductive health have a common aetiology (Skakkebaek, Rajpert-De Meyts, and Main, 2001). However as the number of cases that have both conditions are relatively small it can not be the only aetiology that is associated with either of these conditions. Of the 2,524 cryptorchidism cases that were geo-referenced to the 1991 postcode sectors in Scotland, only 47 babies were also born with hypospadias.

Finally, those covariates that were not found to explain the spatial variation of the cryptorchidism relative risks might also give some insight into the possible aetiology of this condition. Deprivation was not found to explain the spatial variation of cryptorchidism. Deprivation could reflect various possible aetiologies to varying extents e.g. employment (different jobs could have different potential exposures), rural/ urban differences, diet and lifestyle. As these various factors might be associated with cryptorchidism then one measure that encompasses them all is more unlikely to show an association with cryptorchidism risk as the differing factors within the covariate might counteract each other.

The Year of Birth of the cryptorchidism cases was not found to vary spatially, which provides some evidence that the increases in incidence over time of cryptorchidism do not appear to vary spatially. Therefore, while the geographically varying risk factor associated with cryptorchidism might increase over time and so explain the temporal rise in incidence, it would appear unlikely that the rate of change of the exposure varied over geography. Therefore in relation to the proposed aetiology of cryptorchidism and the other anomalies of male reproductive health, if an increasing environmental exposure to oestrogens and/or anti-androgens was responsible for the increase in the incidence of these conditions then it would appear that while the exposure might vary across areas of Scotland the rate of increase of exposure did not vary across the same regions.



The spatial analysis of cryptorchidism cases in Scotland showed a geographically varying risk for this condition of foetal origin. And as first discussed in Chapter 2 and confirmed by this analysis, the cryptorchidism aetiology in Scotland appears to be multivariate and could involve environmental, genetic and life-style factors. This research project was not designed to be able to identify which particular mechanisms would be involved in any changes in male reproductive health but rather to suggest possible aetiology for further investigation.

### **8.1.2 Hypospadias**

To summarise the analysis, the spatial pattern of the relative risks of hypospadias across Scotland is similar to that of cryptorchidism (Figure 138):

- the North East, South-East and South-West areas of Scotland have higher relative risks of hypospadias, and
- the North and the corridor from central Border to the West have lower relative risks.

The spatial variation of hypospadias can, as with cryptorchidism, be partly explained by the rural/urban indicator. The variation of hypospadias risk can also be explained by and one of the radon measurements namely, the proportion of measurements within a postcode area that exceeds 200 Bq/m<sup>3</sup>, but unlike the spatial variation of cryptorchidism it can not be explained by the mean radon level.

As there are similarities in the spatial patterns of cryptorchidism and hypospadias and the covariates that explain their spatial variations, then it suggests some common aetiology. Therefore those potential aetiologies discussed in relation to the spatial variation of cryptorchidism and covariates rural/urban indicators and radon apply to hypospadias and so are not re-iterated here.

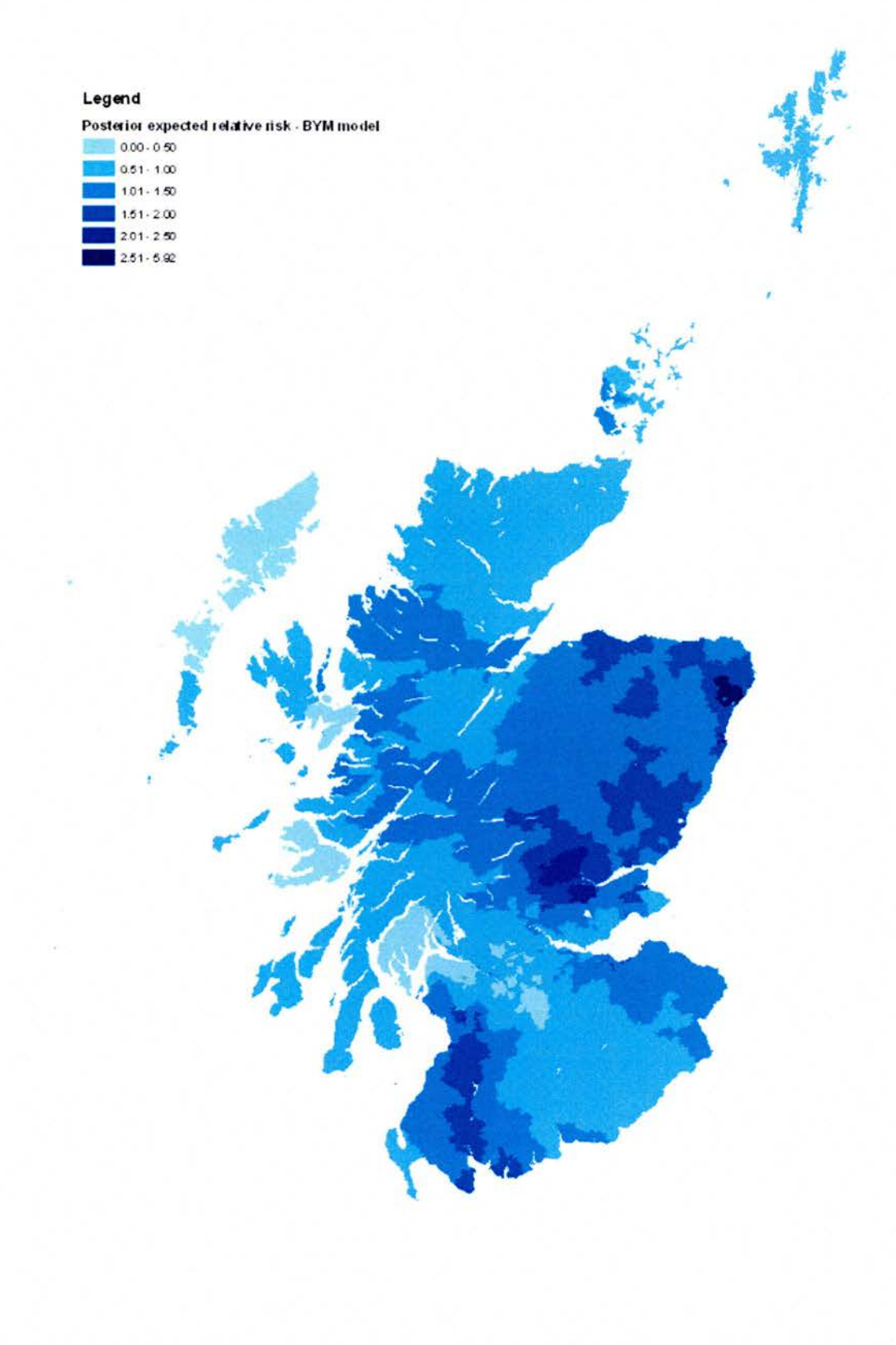
However, these possible risk factors are probably not the only aetiology for these two conditions and other risk factors are perhaps involved that are particular to each. As discussed in relation to the spatial variation of the co-morbidity of cryptorchidism with hypospadias, if a common aetiology was the strongest risk factor for these conditions then we would expect to see a higher number of cases with both

congenital malformations. Only 0.8% of cases in the joint hypospadias and cryptorchidism database used in the project had both conditions (Table 6).

Furthermore, the spatial variation of hypospadias was explained by the excess radon measurement but not the mean radon, while cryptorchidism was explained by both. This could mean that the hypospadias risk could be associated with a threshold dose of radon, while cryptorchidism could be associated with a cumulative dose as well as a threshold effect. Therefore different biological mechanisms would appear to be involved with these two conditions.

Finally, the incidence of hypospadias did not show a general increase with time in Scotland (Figure 92). After an initial increase in incidence of hypospadias the rate fluctuated and then fell so that the number of hypospadias cases were similar in 1995 (9.10 per 1,000 birth) to that in 1980 (8.04 per 1,000 births). Therefore, using consistently collected data, both over geography and time, did not show the same temporal trend in incidence as seen previously (Paulozzi, 1999). This difference could be because the potential ascertainment bias has been removed which accounted for the temporal differences and reflect that the aetiology of hypospadias does not appear to have changed with time. This is contrary to the proposed hypothesis that there has been a decline in male reproductive health, including hypospadias. Providing further evidence that while there is some common aetiology there are some dissimilates in the risk factors associated with these two congenital malformations.

**Figure 138** Hypospadias posterior mean relative risks from BYM model: Scotland (1980-95) by 1991 postcode sector





### 8.1.3 Testicular Cancer

The spatial pattern of the relative risks of Testicular Cancer across Scotland is different from cryptorchidism and hypospadias (Figure 139):

- while the North-East has higher relative risks, as with cryptorchidism and hypospadias, the area of higher relative risks is larger for testicular cancer, including the North, West and a larger area of the South-East,
- the lower relative risks for Testicular Cancer are found in the Central Belt down to the South-East.

As with hypospadias and cryptorchidism the spatial variation of testicular cancer risk can be explained by the rural/urban indicator. Like cryptorchidism, the spatial variation of testicular cancer risk can be explained by the mean radon level Bq/m<sup>3</sup> within each postcode area, although it is not explained by the proportion of measurements within a postcode area that exceeds 200 Bq/m<sup>3</sup>, unlike hypospadias and cryptorchidism.

So while the spatial variation of testicular cancer was different from cryptorchidism and hypospadias, it like these conditions was explained by the rural/urban indicator. Furthermore, the spatial variation of testicular cancer was explained by the mean radon measurements as was cryptorchidism.

Therefore, there is evidence of common aetiology between the three conditions, and as hypospadias and cryptorchidism are of foetal origin this potential risk factor must occur *in utero*. However as the spatial variation is so different for testicular cancer and the potential pathways for exposure are much greater, then these common risk factors do not play as much of a role in testicular cancer's aetiology than that of cryptorchidism and hypospadias.

**Figure 139 Testicular Cancer posterior mean relative risks from BYM model: Scotland (1975-99) by 1991 postcode sector**



The differences in spatial variation of the testicular cancer relative risks compared to cryptorchidism and hypospadias probably reflects both the known aetiology of the condition/diseases and the nature of the geographical data used for testicular cancer. Firstly, testicular cancer incidence mainly occurs decades later than that of cryptorchidism and hypospadias (Bringham and Amato, 2002), which are largely identified at birth or early in a boys life (Kolon, 2002; Duckett, 1998). Therefore, the testicular cancer cases will reflect all potential exposure mechanisms rather than those only occurring *in utero*, which would apply to the cryptorchidism and hypospadias data. Furthermore, the data used for the three indicators reflect this difference as the location of each case is based on incidence. Therefore the location of the testicular cancer cases was recorded when the cancer was diagnosed, while the location of the hypospadias and cryptorchidism cases was the residence of the mother. Consequently the location of the cases reflects the differences in the potential exposure mechanisms experienced by the various disease/conditions and so it is unsurprising that there are dissimilarities in the spatial variation of risk between the congenital malformations and testicular cancer.

From the spatial pattern of the testicular cancer relative risks there appears to be strong rural/urban differences (Figure 139), which is reflected in the rural/urban indicator explaining the spatial variation when included in the Bayesian disease count models. The rural areas have higher risks of testicular cancer compared to the urban areas (except in Aberdeen). As discussed in relation to cryptorchidism, the difference in rural areas between farming and non-farming and types of farming could elucidate if pesticide use is associated with elevated risk of testicular cancer. It would not necessarily mean in the case of testicular cancer that exposure *in utero* is the potential pathway. As already highlighted, the location of the case is at incidence which is typically when men are in their 20's or 30's; therefore potential exposure could have occurred in the meantime. Furthermore, these differences in relative risks between rural/urban areas could also be reflecting a protective effect of living in urban areas and differences in life-style factors (e.g. diet, occupation) between the regions. This is further complicated by the Aberdeen area (on the North-east of Scotland) having higher relative risks for all three of the disease/conditions studied



while being a relatively urban area in Scotland. Therefore it is not so clear cut that there are rural/urban differences in the risk of these conditions.

Finally, there does appear to be a temporal increase in the incidence of testicular cancer in Scotland in the last 25 years for which data are available (Figure 61), which supports previous studies (Adami *et al.*, 1994; Bergstrom *et al.*, 1996; McKiernan *et al.*, 1999). Furthermore, that there is an age cohort effect on the incidence rates in Scotland, which again corresponds with the known aetiology of testicular cancer (Bringinghurst and Amato, 2002; Buetow, 1995; Robbins *et al.*, 1999). Those age groups with the higher incidence (20 to 49) also experienced the highest rate of increase of incidence over time. Therefore whatever exposure is resulting in the increase in incidence of testicular cancer in these age groups, it is likely to be what is changing the incidence rates overall. As seen in the review of the morphology of testicular cancer, age is related to morphology type and the majority of cases are germ cell neoplasms (Bringinghurst and Amato, 2002; Buetow, 1995; Robbins *et al.*, 1999). Therefore particular morphology groups of testicular cancer are showing the temporal increases and so further investigation of the aetiology and morphology of these types of testicular cancer could elucidate potential mechanisms.

### 8.1.4 Combined analysis of the three indicators

From the conjoint spatial analysis of the three conditions the spatial patterns produced for cryptorchidism and hypospadias are similar to those produced by the separate models, but altered for testicular cancer.

The spatial pattern of the relative risks of cryptorchidism produced by the conjoint model is similar to that produced by the individual cryptorchidism models (Figure 140):

- higher relative risks of cryptorchidism can be found in the East and South-West areas of Scotland as previously but also in the North, while
- lower relative risks of cryptorchidism are still found in the corridor from central Borders to the West Coast.

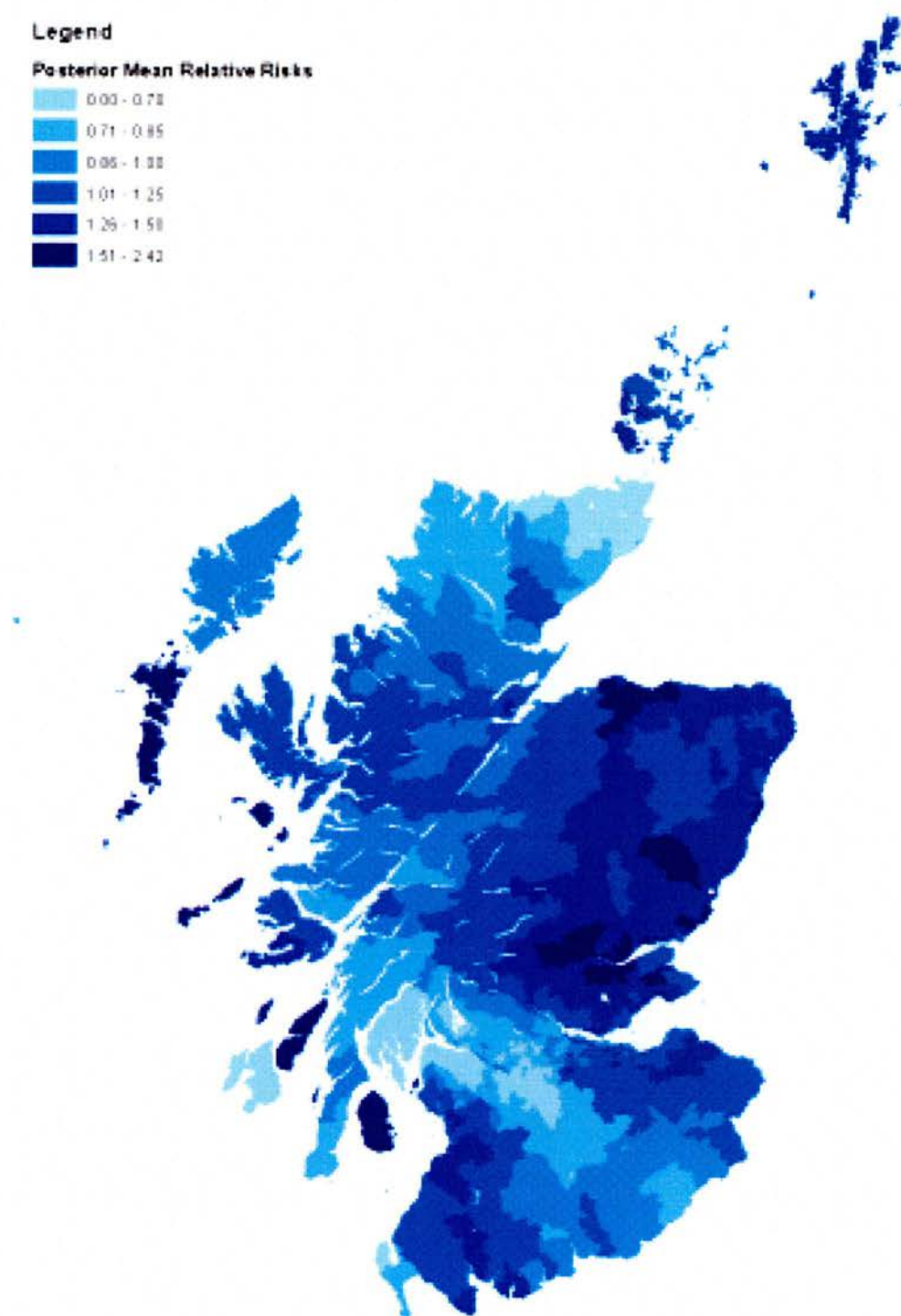
The spatial pattern of the relative risks of hypospadias produced by the conjoint model is similar to that produced by the individual hypospadias model and so is similar to that of cryptorchidism (Figure 141):

- higher relative risks of hypospadias can be found in the North, North East, South-East and South-West areas of Scotland, and
- lower relative risks of hypospadias are found in the corridor from central Borders to the West Coast.

The spatial pattern of the relative risks of testicular cancer across Scotland is considerably altered when estimates produced by multi-indicator model (Figure 142). There are:

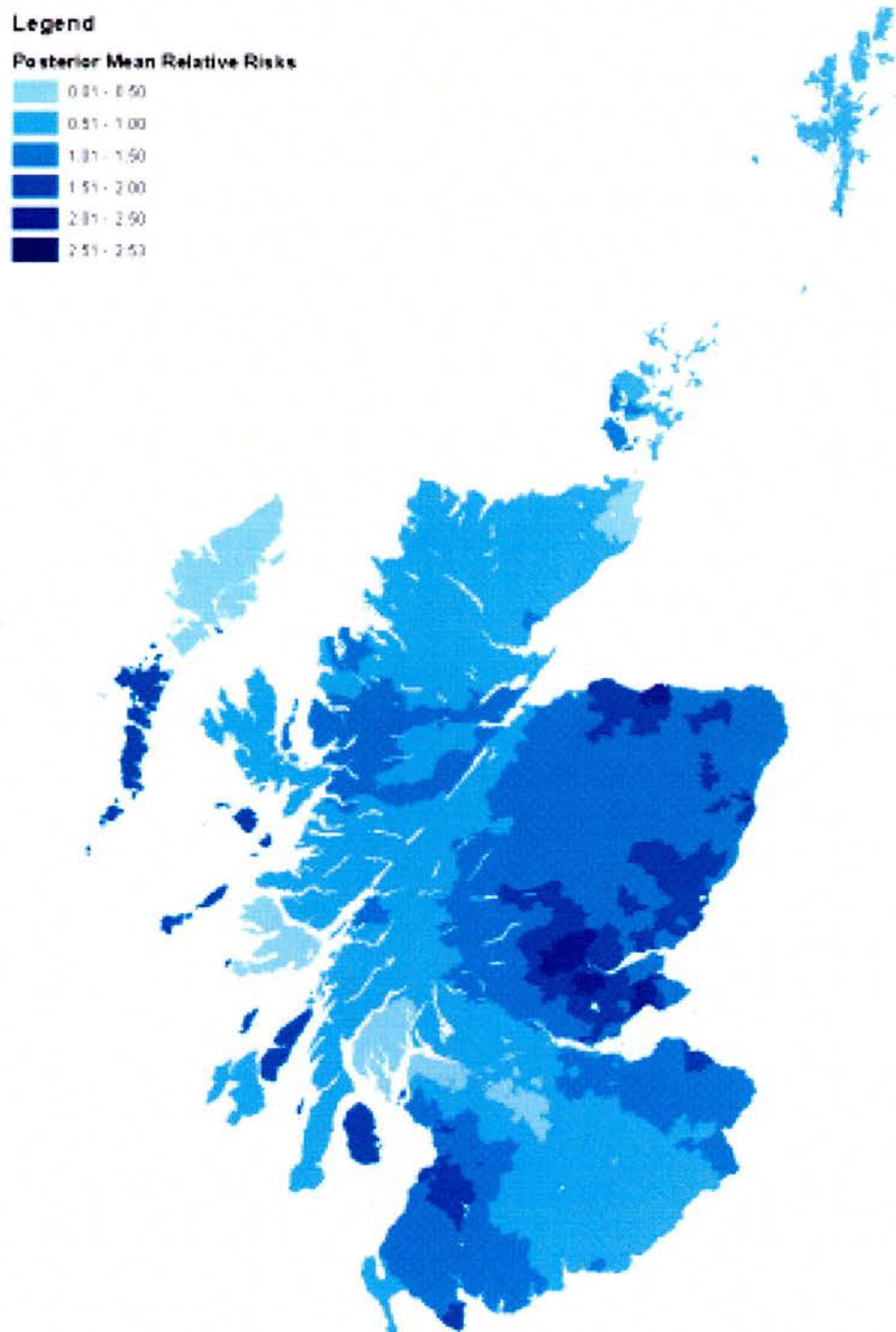
- clusters of higher relative risks in the North, North-East, South-West, and
- clusters of lower relative risks in the South East and West.

**Figure 140 Cryptorchidism multi-indicator model (with both heterogeneity terms) results: posterior estimates of relative risks by 1991 postcode sector, Scotland 1980-95**

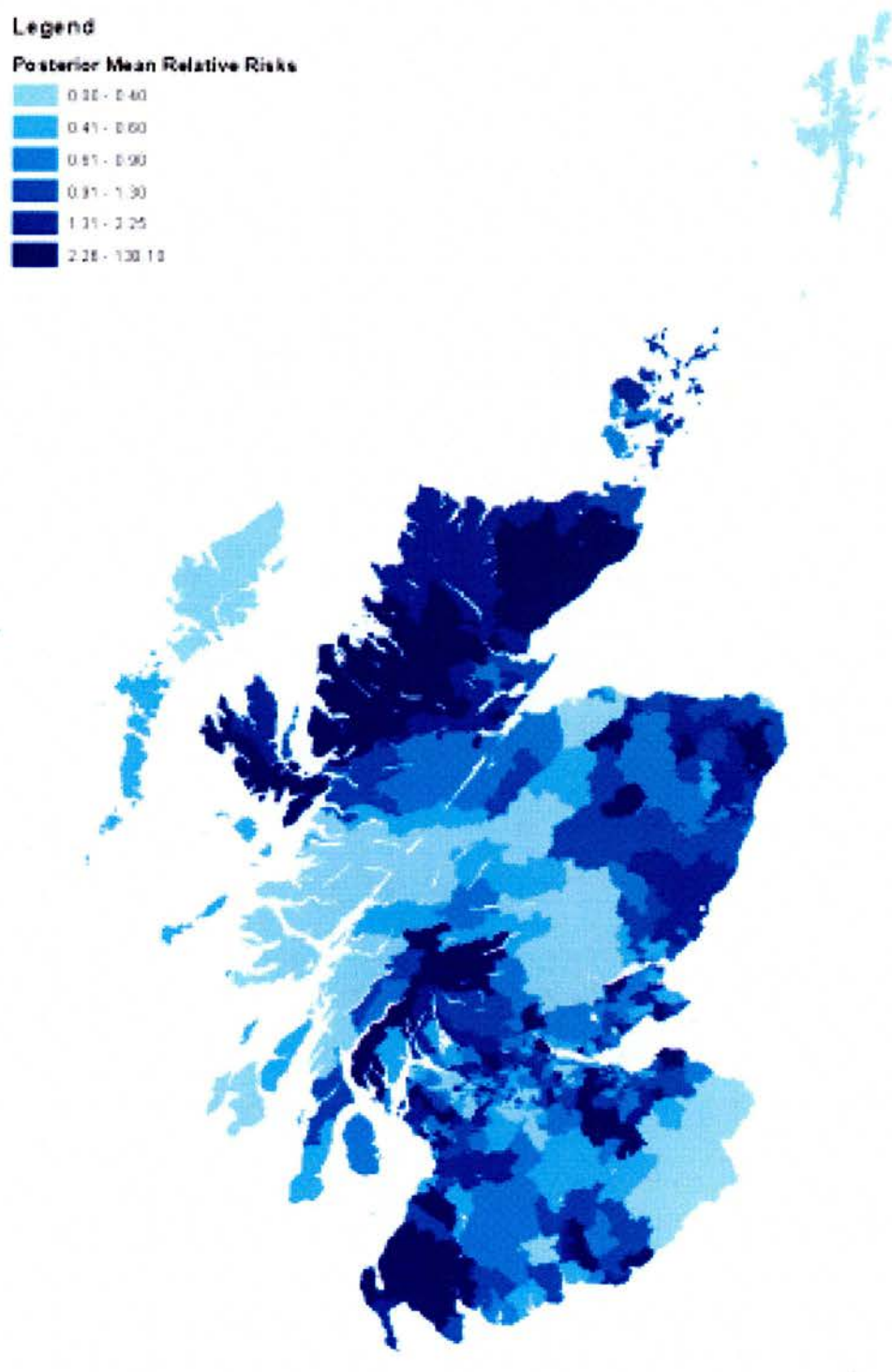




**Figure 141** Hypospadias multi-indicator model (with both heterogeneity terms) results: posterior estimates of relative risks by 1991 postcode sector, Scotland 1980-95



**Figure 142 Testicular Cancer multi-indicator model (with both heterogeneity terms) results: posterior estimates of relative risks by 1991 postcode sector, Scotland 1975-99**



From the conjoint analysis of the three indicators of male reproductive health there would appear to be a shared geographical pattern of risk between cryptorchidism and hypospadias, but not between them and testicular cancer.

One benefit of the multi-indicator model, as detailed in Section 3.8, is to reduce the variability of the estimates of the relative risk as within each postcode sector every disease/conditions borrows strength from other disease. The potential power gain only applies when the spatial patterns of the indicators included are similar, which applies to cryptorchidism and hypospadias. Therefore, more robust estimates of the relative risks for cryptorchidism and hypospadias show the same pattern as the individual disease models and so the possible aetiology discussed for both conditions earlier is still applicable. In particular, there is evidence to show that there is some common geographically-varying aetiology between the two congenital malformations.

The similarities in spatial pattern of the relative risks of cryptorchidism and hypospadias were confirmed by the correlations produced by the multi-indicator model. The correlation of the unexplained risk between these two conditions was strongly spatially structured ( $r = 0.97$ ). So there is a relationship between the risk of these two conditions and a shared spatially-varying risk factor. So in line with the hypothesised aetiology this research has shown that there is a common aetiology between these two conditions. However, as seen in the outline of previous research of male reproductive health and the discussion of the results for these conditions this common aetiology could be environmental exposure and also various other potential risk factors. Furthermore, the difference between the spatial pattern of these conditions and testicular cancer does highlight that other potential mechanisms are involved in the subsequent development of these anomalies.

As noted in the conclusion of the conjoint analysis chapter, the testicular cancer data would appear to be a poor fit to the multi-indicator model. This was due to the different spatial pattern of the testicular cancer risk compare to cryptorchidism and hypospadias. And as discussed in relation to the spatial analysis of the testicular cancer risk, these differences in spatial variation of the testicular cancer relative risks could reflect both the known aetiology and the nature of the geographical data used



for testicular cancer. Therefore, the difference in the spatial variation of testicular cancer risk reflects all potential exposure mechanisms rather than those only occurring *in utero* which would apply to the cryptorchidism and hypospadias data.

In the paper that first outlined the TDS hypothesis, the authors proposed that while the overall incidence of TDS decreases with its severity, the relative incidence of testicular cancer increases while the relative incidence of the other conditions decrease (Skakkebaek, Rajpert-De Meyts, and Main, 2001). Do these proposed relationships between the disease/conditions of TDS correspond with the results of this research project?

From these statements we would expect a negative spatial correlation between either cryptorchidism or hypospadias and testicular cancer, as the relative incidence of these conditions are proposed to decrease with an increase in testicular cancer. This is not the case with these results – a small positive correlation was found rather than a strong negative (Table 49). However, as already discussed the testicular cancer data was based on incidence rather than potential exposure therefore the spatial relationship between testicular cancer and cryptorchidism and hypospadias has been compromised and can not be compared directly with these data. It is proposed that the incidence of TDS decreases with severity and that the relative incidence of cryptorchidism and hypospadias also decrease. Therefore expect inverse relationships between these conditions and any exposure, as we would expect the relationships to mirror that between severity and exposure. However in the analysis of the disease/conditions this would appear not to be the case – those areas we expect to have higher levels of pesticides (i.e. rural) are in the main those areas with higher relative risks of cryptorchidism or hypospadias. Therefore these data do not follow the proposed relationships outlined in the TDS hypothesis.

## **8.2 Limitations of results and research project**

In order to fully evaluate the conclusions made from the spatial analysis, the limitations of this research project need to be discussed. The limitations can be grouped into two categories: the data used in the research project; and the analysis carried out.

### **8.2.1 Data Issues**

Specific issues concerning the data used were raised from the analysis and might have implications for the conclusions made.

#### **8.2.1.1 Cryptorchidism and Hypospadias**

Although the data used for these two conditions has been collected consistently over geography and time in Scotland, and so overcoming the limitations of previous work, there are two issues highlighted from the analysis that need to be considered.

For each of these condition when the cases were re-assigned to the 1991 postcode sectors, there were a high number of records in one area of Scotland where the Local Council was recorded instead of the postcode sector. As these records could not be geo-referenced they were excluded from the spatial analysis. Therefore there would be underreporting of cases in the postcode sectors covered by Kirkcaldy, North East Fife and Dunfermline. This could have meant that the relative risk estimates for these areas would be lower than should be. However, as the denominator data used to calculate the expected values were based on the same datasets, the same level of under-reporting in Kirkcaldy, North-East Fife and Dunfermline of total birth events was seen. Therefore the impact of under-reporting in these areas would have been minimised in the resulting relative risks/SMRs.

Under-reporting will also have occurred if cases of hypospadias and cryptorchidism have not been identified at birth but later in the boy's life. As the datasets used for these conditions were based on births then those cases would not have been included. From the current knowledge of these conditions this will have been of greater impact to the cryptorchidism data than the hypospadias. As discussed in Chapter 2, due to differing clinical practice a cryptorchidism case might be left to see if testes descend of their own accord (Kolon, 2002); while hypospadias is largely treated by surgery and clearly identified at birth (Duckett, 1998). Furthermore, those cases ascertained at birth might be different from those determined later for both conditions. For instance, milder cases that would be more likely to be identified later might have a different aetiology than the more severe cases. It might be possible to assess the size of this potential under-reporting by comparing the case ascertainment in these datasets with other local congenital abnormality registers. However, according to



sources at ISD these registers are not consistent over geography and time and so this exercise would only be able to estimate a lower limit of the under-registrations. As the proportion of under-reporting might be linked to clinical practice their levels might be different with geography and time.

It should be remembered that while an advantage of the data used is that it is of high quality and is consistently collected over the study region and time, we can not be certain that differences in ascertainment could explain the spatial variation in risk. Apart from those just discussed other differences in case ascertainment/reporting between hospitals could be at play and we are unaware of them.

#### **8.2.1.2 Denominator Data**

As discussed in relation to cryptorchidism and hypospadias the birth data would be affected by under-reporting in Kirkcaldy, North-East Fife and Dunfermline. However as already mentioned, the impact on the relative risks estimated might be minimised as the number of cases were under-reported in the same areas for the same reasons.

As the population data used to standardise the testicular cancer cases is based on Census data there are issues with respect to under-reporting. According to GRO Scotland the under-reporting of the population was 2% in the 1991 Census. However the population data used in this project had been adjusted for under-reporting dependent on the following groups within areas: the elderly, those aged 20-24 or those areas in the inner-cities, as these groups/areas were assessed to be most affected by under-reporting.

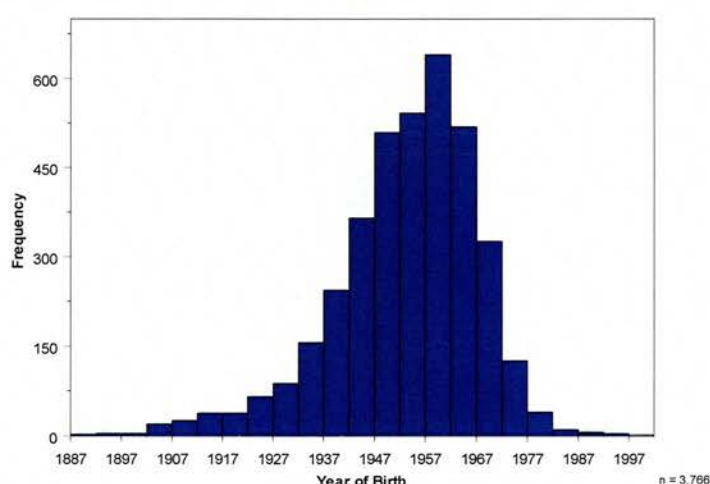
#### **8.2.1.3 No birth postcode sector data for testicular cancer**

As already noted both in assessing the spatial variation of testicular cancer and its inclusion in the conjoint analysis, the testicular cancer cases' spatial location were based on incidence postcode, which was typically decades after birth and therefore probably at a different location to that at birth. Therefore the spatial variation of the testicular cancer represents all the potential pathways of exposure rather than just those *in utero* and includes possible migration. To investigate if *in utero* aetiology is associated with testicular cancer it would be necessary to find out the place of birth of the testicular cancer cases.



This was considered at the beginning of the research project and a possible solution was found. At that time it was stated that ISD could match the testicular cancer cases to corresponding birth records, so as to obtain the postcode sector of mother's residence at birth. However it became apparent that birth data was only available electronically for births in 1974 onwards. As can be seen, the majority of testicular cancer cases in the dataset were born in the 1940's through to the 1960's and only a small proportion (3%) were born since 1974 (Figure 143). Therefore for the majority of testicular cancer cases it was not possible to match electronically to birth location.

**Figure 143 Distribution of Year of Birth for testicular cancer dataset**



It would have been possible to obtain the mother's place of residence at birth by searching manually the microfiche birth data records. However, it would have taken approximately 52 weeks full time to complete this task. There are plans underway within GRO to digitise birth records back to 1855, but this would not be available until the end of 2004. Therefore, the spatial analysis of the testicular cancer dataset was based on the location at registration.

To investigate if *in utero* risk factors are associated with testicular cancer incidence the matching of testicular cancer cases to place of birth and subsequent analysis could be done in the future.

#### **8.2.1.4 Different time spans of disease/condition datasets**

There were differences in the time-spans of the datasets included in the multi-indicator models that might impact on the subsequent results. Cryptorchidism and hypospadias cases span births from 1980-1995, while testicular cancer cases span incidence from 1975 to 1999. Firstly, the larger number of years covered by the testicular cancer dataset would mean that higher number of testicular cancer cases was included than if it had been testicular cancer incidence from 1980 to 1995. Therefore, there might be over-representation of testicular cancer cases in the multi-indicator model. Furthermore, as this was testicular cancer incidence, than as seen in Figure 143, this represents births spanning 1887 to 1995. So if a birth cohort effect is associated with these three conditions the birth cohorts are not comparable between the datasets.

#### **8.2.1.5 Potential Covariates**

Issues were raised from the analysis concerning particular covariates that might have consequences for the conclusions.

As already highlighted the rural/ urban indicator was a proxy for attempting to see if farming areas, a source of pesticides use, have an association with the spatial variation of the relative risks of the three conditions. However as a proxy for pesticide exposure it has limitations which need to be discussed. While a rural/urban indicator will show which areas are 'rural' or 'urban, there are many other factors apart from pesticide use that differentiate between those areas. As already discussed in 8.1.1 in relation to cryptorchidism, the various factors (e.g. diet, lifestyle, occupation) might have different impacts on health in general and male reproductive health specifically. Furthermore, this rural/urban indicator is actually measuring the population density of areas and so farming areas might not always equate to less densely populated areas or indeed to rural areas, particularly in Scotland.

Therefore other data would be better placed to explore pesticide use and other potential endocrine disruptors association with the spatial distributions of these disease/conditions. For instance, within the Census the percentage of the population farming might be a better proxy, as it indicates actual farming areas rather just rural areas. It would however still be a proxy, i.e. it does not indicate if a farming area uses



pesticides or other chemicals. As the use of pesticides etc. would be dependent on what type of farming was undertaken, another possible data to investigate would be land use/cover data which are available from the Countryside Survey ([www.cs2000.org.uk](http://www.cs2000.org.uk)). These data could indicate different types of farming (arable, livestock) that are likely to use different types of chemicals (e.g. herbicides and phosphates). At present the associations found between rural/urban areas and the indicators of male reproductive health are limited by the indicator used, to be able to confirm an association between pesticide exposure and subsequent decline in male reproductive health. To investigate the association between farming/pesticides and male reproductive health these potential covariates should be used, and would have been in this research project if this researcher had been aware of them.

While unaware of the data just outlined, other information that would also have been important potential covariates was not included in this research project for other reasons. As summarised in Table 8, various potential covariates were not included due to lack of availability to this researcher and in the appropriate format. Therefore to show how environmental data could be used in the spatial mode, radon data were included. As admitted in 3.4.5.3 there are no previous research to show an association between male reproductive health and radon, and while associations were found between radon and the disease/conditions, it is more likely due to other reasons than aetiology. Firstly, there might be confounding between the rural/urban indicator and radon. Those regions that show high levels of radon are on the whole rural areas and vice-versa. Therefore, the radon measurements might have associations with the disease/conditions because of their association with the rural/urban indicator. Further development of the spatial models as outlined in 8.3.1.4 could explore possible confounding.

Furthermore, the spatial resolution of the radon measurements could have had an impact on its apparent associations with the disease/conditions. As the radon measurements are at postcode area levels and one of the areas with the highest levels of radon (NE Scotland) is also one of the areas with the highest risks of cryptorchidism, hypospadias and testicular cancer, then the spatial association found could just mirror this rather than actually explain aetiology. Therefore to fully



explore if there are spatial relationships between radon and male reproductive health, we would require radon data at a higher spatial resolution, which will be available soon for the North East, where the highest levels of radon in Scotland can be found (NRPB, 2003).

Further discussion of potential covariates which could be included in future analysis can be found in 8.3.1.

## **8.2.2 Analysis Issues**

There are particular issues that arose from the analysis that need to be considered.

### ***8.2.2.1 Establishing a Common Geography***

As outlined in Section 3.5, it was necessary to re-assign postcode sectors to those valid as at 1991 Census. This resulted in a small proportion (3.7%) of the postcode units been mis-assigned to neighbouring postcode sectors. This could potentially have resulted in particular postcode sectors having less or more cases depending on if they were a postcode sector that gained a postcode unit or lost one. As we are dealing with areas with small number of cases this could have changed the relative risks in particular postcode sectors considerably. The birth denominator data used for cryptorchidism and hypospadias relative risks also had to be re-assigned to 1991 postcode sector boundaries, and the same mis-assignment of these data occurred. Therefore, the potential disparity between the observed and expected values is likely to be minimised. However this potential minimisation of the mis-assignment effect does not apply to the testicular cancer cases as the population data was already assigned to 1991 postcode sectors.

### ***8.2.2.2 Performance of Bayesian Hierarchical Disease Count Models***

In each of the individual disease/condition spatial analysis as disease count data, none of the three Bayesian Hierarchical models used were completely appropriate at fully explaining the datasets. Each Bayesian Hierarchical model smoothed the crude relative risks (SMRs) and so reduced their variability for each disease/condition. However from the analysis of the residuals for each model, none were able to successfully fit the higher relative risk values.

Although the best of the three Bayesian Hierarchical disease count models was the BYM according to the DIC results, there were concerns raised about the spatially correlated heterogeneity term used within it. While the assumption that the heterogeneity of the estimates might be spatially correlated is a valid one i.e. a particular postcode might be similar to its neighbours, the implementation of this term within WinBUGs has raised concerns. As seen in the visual assessments of the spatial variation of the relative risks produced by the Bayesian Hierarchical models and the comparison of the Log-Normal and BYM models with the inclusion of covariates it is unclear if the spatially correlated heterogeneity term might actually over-smooth the spatially correlated heterogeneity. Particularly in the case of the testicular cancer data, the stark difference in the spatial variation of the relative risk estimates produced by the Log-Normal and BYM models does suggest that the spatially correlated heterogeneity term included in the BYM model over smooths the spatially correlated variability of the estimates. Furthermore, failure of potential covariates to explain the spatial variation of the estimates from the BYM model after explaining the variation in the estimates of the Log-Normal model suggest that any variation in the data had already been ‘soaked up’ by the spatially correlated heterogeneity term. Finally, the sensitivity analysis carried out on the BYM within each disease/condition that compared the relative risks produced by the BYM model and the same model with a less specific prior for the precision of the spatially correlated heterogeneity, showed that the prior used did not explain the over-smoothing of the relative risks.

Further analysis and development of the CAR model’s performance, and the spatial Bayesian Hierarchical models used WinBUGs is needed. Indeed as yet unpublished work has shown that another model known as the Lawson & Clark model has been found to perform better than BYM in particular cases (Hossain and Lawson, 2005). Spatial analysis using Bayesian methods is still a relatively new field and the development of appropriate models is still ongoing.

For the spatially correlated heterogeneity term used in this research project it would have been possible to add multiple levels of neighbours i.e. not only direct neighbours to a postcode sector but also those next to the neighbours. While these



could have been added with the appropriate weighting, it was felt that as the spatially correlated heterogeneity term was already appearing to over-correlate the estimates then it might not have been appropriate.

#### **8.2.2.3 Performance of multi-indicator model**

While the multi-indicator model outlined in 3.8 is based on a previously specified model (Knorr-Held and Best, 2001), as it was extended to include three diseases rather than the original two, there are limitations and problems associated with its use in this research project.

Firstly, the large number of nodes to be estimated using a modest amount of data resulted in requiring a considerable number of iterations (20,000) to obtain stable estimates of the relevant nodes. Indeed running of the multi-indicator models would take several days on the PC and no other computer packages could be used concurrently during this time or WinBUGs would crash.

These time and processing constraints limited the development of the multi-indicator further. For instance, no sensitivity analysis of the hyper-priors was carried out on these models. This analysis would be important as it is a relatively new model and has not previously been extended to use three diseases. Furthermore with a large number of nodes to estimate and comparatively modest data to use the resultant nodes would probably have been dependent on the hyper-priors specified.

#### **8.2.2.4 Edge effects**

Edge effects in spatial analysis occur due to the proximity to the study window edge. The spatially correlated heterogeneity term correlates a specific postcode sector's relative risk estimate to its neighbours. But for those postcode sectors which are on the edge of the study window there are neighbours which are not included in this. In this research study, this would only concern the Borders of Scotland as the remaining edges of the study window are coast or islands, and so do not have any neighbours. The two basic methods of dealing with edge effects (1) use of weighting correction systems or (2) guard areas were not employed. Therefore the estimates in the Border region estimated by the BYM model could have been re-estimated, dependent on which method of dealing with the edge effects were used and the assumptions made about the unknown areas.



### **8.2.2.5 Spatial Resolution Implications**

There are particular analysis issues raised from this research project that are relevant to all spatial epidemiological studies that use disease count data. Due to interpretations of data confidentiality legislation the spatial resolution of the disease/condition data was at postcode sector rather than the preferred full postcode unit. The use of the data at this resolution had an impact on the analysis carried out and so on the subsequent conclusions.

Firstly, as already discussed the postcode sectors had to be re-assigned to one common geography and this resulted in some cases being mis-assigned. If full postcode unit had been provided the assignment to the postcode sector boundaries would have been carried out without that potential mis-assignment. Furthermore, if the postcode unit of each case had been provided the potential problems of what is known as the ‘modifiable area problem’ would not have been relevant. This occurs when the use of different boundary systems can result in clusters either been masked or fabricated and is a potential consequence of using aggregated data, i.e. a particular postcode sector might have high number of cases just because of the boundary location, and a slight change might result in the case in that postcode sector been dispersed to neighbouring postcode sectors. This is very much related to the issue of ecological fallacy which was discussed in detail in Chapter 3.

If the disease/condition datasets had been provided at postcode unit level the possibility of ecological fallacy would have been greatly reduced. As seen from the cryptorchidism individual analysis, the possibility of ecological bias can not be ruled out with these data. This bias is a considerable limitation to the analysis of disease count data.

The potential for confounding also needs to be discussed in relation to aggregated data. In the context of the research study, the geographical variations found in the analysis may well be due to geographical varying environmental agent. However, there might be a non-environmental factor(s) that accounts for the geographical variation that has not been included in any of the spatial models. Furthermore, the covariates that appear to explain the geographical variations within the analysis might mirror the spatial variation of the disease/condition model and another

covariate that has not been included. Further spatial analysis is required to overcome some of these issues.

## **8.3 Future Research**

This research has shown that there are geographical variations to the three disease/conditions in Scotland and has indicated possible aetiologies for further investigation. Apart from highlighting the complex nature of these conditions and the potential pathways for exposure to possible risk factors, there are as with any research, other questions and issues that require further investigation. The issues that are discussed here stem from the research project but are in the context of current male reproductive health research. Some of this potential future work have already been raised in the previous discussion and so are only summarised here. Those issues not raised previously are discussed in more detail.

### **8.3.1 Potential Covariates**

As already mentioned further analysis of data pertaining to rural/urban differences and radon measurements are required to further assess if these risk factors are associated with these disease/conditions. Furthermore, the research project only included five covariates for investigation. Therefore apart from the further analysis of potential covariates previously mentioned other area-specific covariates could have been included in the Bayesian models to explain the spatial variation of the three disease/conditions. The covariates suggested here are far from exhaustive but rather that they have been highlighted by current male reproductive health or have arisen as a result of this research project.

#### **8.3.1.1 Smoking**

Previous research has found an association with poor health of resulting children and women smoking while pregnant (DiFranza, Aligne, and Weitzman, 2004). Specifically in terms of male reproductive health, recent research has found that men's subsequent semen quality can be adversely affected if his mother smoked while pregnant with him (Jensen *et al.*, 2004). If information concerning mother's smoking status could be found it might be included in either the disease count models or as individual assessment of spatial variation.



In order to see if mother's smoking status explains the spatial variation produced by the Bayesian Hierarchical Models we require information at postcode sector level. The Census's do provide the proportion of people who smoke within a postcode sector, although it does not appear to ascertain the proportions that are pregnant women. Therefore, this area-specific information on smoking would be a proxy for the exact information required, but might indicate if there is some association.

As seen in the file format of the cryptorchidism and hypospadias data the smoking status of these cases was recorded (Appendix 1). However, an individual model was not developed for the cryptorchidism cases for this covariate as it was poorly completed. This record was not compulsory and less than a third of cryptorchidism cases were completed appropriately. Therefore, it would not have been suitable to develop a model to assess the spatial variation of this covariate, to see if it was similar to cryptorchidism relative risks.

#### **8.3.1.2 Genetic predisposition**

As seen from the discussion of the analysis, the possible spatial variation of the three conditions might in part be due to the underlying genetic differences in the Scottish population. Therefore, genetic information that is geo-referenced would be required to explore any association with this and the spatial variation in risk of the three disease/conditions. However, other types of epidemiological studies might be more appropriate to explore genetic associations.

#### **8.3.1.3 Environmental chemicals exposure**

While the TDS hypothesis postulates that male reproductive health has deteriorated due to increasing exposure to oestrogens and/or anti-androgens, no covariate has been included in the analysis in relation to 'environmental chemicals'. As discussed in 3.4.5 the geo-referenced environmental data available to this researcher was limited, either across Scotland or at appropriate spatial resolution. Further investigation for data on sources of human exposure to endocrine disruptors across Scotland is required, as this is the key explanatory factor. As well as those data discussed in relation to an alternative to the rural/urban indicator used in the research project (8.2.1.5), other data that stem from the review of potential sources of human exposure to endocrine disruptors (2.3.2 and Table 2) and the discussion of how these



potential covariates were identified and selected (3.4.5), would need to be explored further. Table 51 summarises those data that have been brought my attention since completion of the analysis was completed that require further investigation.

**Table 51 Data requiring investigation on suitability to be included as potential covariates concerned with sources of human exposure to endocrine disruptors**

Data	Description	Source
Air Pollution emission data	Concentration of chemicals (e.g. sulphur dioxide and nitrogen oxides) from industrial sites etc. across Scotland - create emission maps	Scottish Environment Protection Agency
Air quality data	Concentrations of air-borne particulates (e.g. nitrogen dioxide and sulphur dioxide) from sample sites across Scotland – create air quality maps	UK National Air Quality Archive
Drinking Water data	% of samples failing coliform test (indication of breach of water supply) – create drinking water quality maps	Scottish Executive Drinking Water Quality Division
River Water Quality Data	Digitised River Network (DRN) that classifies quality of a quarter of Scotland's river network (i.e. the major watercourses). Also contains concentration levels (e.g. nitrates and orthophosphates) - create river water quality maps that could be incorporated into water distribution map	Scottish Environment Protection Agency

#### **8.3.1.4 Associations between covariates**

Also highlighted by the proposed TDS hypothesis is that a genetic-environmental interaction might explain the proposed deterioration in male reproductive health. This highlights that there is probably associations between risk factors which has not been accounted for in this research project. Not only would there likely to be associations between the covariates included in the analysis (e.g. deprivation and rural/urban differences) but also between them and other proposed covariates (e.g. deprivation and smoking). Therefore, to attempt to fully account for the various risk factors that might be associated with these conditions, these associations would have to be included to the Bayesian Hierarchical models.

#### **8.3.2 Other indicators of male reproductive health**

This research project included three of the disease/conditions that are believed to have increased in incidence in the last few decades. The spatial variation of these three indicators was carried out as the data were collected consistently over geography and time. However other indicators could have been analysed, as they too

are believed to have been affected by the same aetiology as testicular cancer, cryptorchidism and hypospadias.

#### **8.3.2.1 Semen Quality data**

As seen in Chapter 2 the previous research that shows a decline in semen quality over the last few decades remains controversial. While a spatial analysis of semen quality would not address this issue, the exploration of the semen quality in a country might, as we have seen in this research project, highlight possible aetiology for further investigation.

In order for this to be accomplished semen quality data are required from a randomly selected group of the population. This would mean that the data would hopefully represent the general population rather than particular sub-groups, so overcoming criticisms of previous research. As already noted, a population based study of semen quality has just been completed in Scotland. Spatial analysis of these data could provide insights into the possible aetiology of semen quality. As with testicular cancer, semen quality aetiology is complicated by the various potential pathways for exposure to risk factors, as it is largely only ascertained when men are in their 20's and 30's. The population based study in Scotland includes information on the various stages of a man life and looks at the various potential risk factors which could also be included in any spatial analysis.

However the spatial analysis of the semen quality would have to employ very different methods from those shown in this research project. While disease data used here are count data i.e. the number of cases within a particular postcode sector, the semen quality would be a particular semen quality measurement for a particular individual at a specific location. Therefore the inclusion of the semen quality to a multi-indicator model would require further developments in spatial models methodology.

#### **8.3.2.2 Birth events data**

Although not included in the review of previous research concerning male reproductive health, some studies looking at the changes in sex ratio of births and numbers of twins have also been used to argue that changes have occurred in these birth events and that these too are related to the TDS hypothesis.



Both indicators, twin births (Lloyd et al., 1988; Lloyd, Lloyd, and Holland, 1984) and sex ratios of live births (Williams, Lawson, and Lloyd, 1992) have been used previously to assess the impact of air pollution caused by industry on the surrounding area. Furthermore, these indicators have been used by other authors to support the TDS hypothesis as it is believed that both are affected by the intrauterine environment (Moller, 1998). However, as with other anomalies of male reproductive health there are other factors that are associated with these two indicators that mean the assessment of their possible aetiologies is complex.

As discussed by Williams *et al.* (1992) the sex ratio of births (male/female) is not static and can vary geographically, and can be affected by exposure to pollutants in the air, by age and blood group of mother, season of the year, exposure to Hepatitis B, exposure to pollutants in the water and paternal occupation. It is believed that the mechanisms which cause the ratio to vary are also related to the hormonal levels of the mother and father. As with the sex ratio, twinning rates are also influenced by genetic and environments factors such as maternal age, parity, height of mother, geographical variation, seasonality, genetics and infertility treatment (Derom et al., 1995). Furthermore, there also appears to be a relationship between sex ratio and multiple births. Derom *et al.*, (1995) reported that the proportion of males decreases with each increase in the number of fetuses per pregnancy.

Data on both these birth events are collected consistently over geography and time and are available at postcode sector level in Scotland. Indeed, the data was requested as part of the denominator data used for the cryptorchidism and hypospadias relative risks. Therefore, the investigation of the spatial variation of these two indicators is possible in Scotland and would add to the analysis already carried out. However, as with the anomalies analysed in this research project the various other risk factors that are associated with these events also have to be accounted for.



### **8.3.3 Future development in Bayesian Spatial Analysis**

There are a number of issues highlighted from the analysis that stem from the particular Bayesian Hierarchical Model used that require further development.

#### ***8.3.3.1 Disease Count Models***

As already discussed, the further development of models of disease count models is required. For example, the spatially correlated heterogeneity term in the BYM model does appear to over-smooth the heterogeneity. Furthermore, there is evidence that the Lawson & Clarke model appears to be more appropriate than the BYM model in particular circumstances (Hossain & Lawson, 2005). This is an emerging field and so the development of disease count models in a Bayesian context is continuing.

#### ***8.3.3.2 Inclusion of Individual level information***

The individual level spatial analysis was carried out only on a subset of the cryptorchidism dataset; and not on the hypospadias and testicular cancer datasets. To fully assess the impact of individual level information on these three disease/conditions further, spatial analysis of these potential covariates are required; not just the covariates included in disease/conditions datasets but also other relevant individual information e.g. complete data on mother's smoking status, diet and occupation.

While the cryptorchidism individual level analysis highlights that individual factors may explain the spatial variation in disease risks it does not give direct relationships between individual covariates and the spatial variation of cryptorchidism. Therefore, the development of Bayesian hierarchical disease count models that could include both individual and area level covariates is a methodological issue which needs to be resolved. The need to test for the possibility of ecological fallacy is crucial in disease count models and therefore a model that could include both area and individual specific covariates would be appropriate. Furthermore, as seen in male reproductive health research, and applicable to many other areas of health research, there are area and individual specific risk factors that might explain the spatial variation of these conditions. Therefore a model that included both area and individual specific covariates would more realistically reflect the potential aetiology.

### **8.3.3.3 Multi-indicator models**

An analysis that might give further insight into male reproductive health would be the development within the multi-indicator model of one measure for all the indicators. As already discussed, more spatial analyses are now being carried out jointly on more than one disease. The common burden of disease caused by a particular environmental factor is not an uncommon aim of research e.g. a putative health hazard might have an impact on a number of health indicators. Therefore for the development of a joint measure of more than one disease/condition would provide insights into the common burden of disease and so aetiology.

### **8.3.4 Future directions for male reproductive health research**

In 2.3.1 the Bradford Hill criteria were used to assess if the Skakkebaek and colleagues paper that outlined the TDS hypothesis, also proved causality (Hill, 1965; Skakkebaek, Rajpert-De Meyts, and Main, 2001). These criteria can also be used to assess if this research project has fulfilled the hypothesis that *in utero* exposure to oestrogens and/or anti-androgens results in various symptoms of TDS.

This research project was able to show that the three indicators of male reproductive health have geographical variation and so appear to have geographically varying risk factors associated with them. Furthermore, as the spatial variation of cryptorchidism and hypospadias is similar it is likely that they have some common aetiology which must occur *in utero*. As the same risk factors were found to be associated with testicular cancer and the congenital malformations, then this carcinoma appears to share some aetiology with cryptorchidism and hypospadias. Therefore there are geographically varying risk factors whose exposure occurs *in utero*, that are associated with all three conditions, providing some evidence to support the proposed hypothesis.

However, the common aetiology of these conditions could not only be environmental but also due to genetic and life-style factors, that could pertain to the individual cases rather than the specific area. Furthermore, the limitations of the potential covariates used in the research project mean that further analysis with more robust data is required. Therefore, while this research project lends some argument that *in utero* risk factors are associated with these conditions it was not able to prove



causality i.e. *in utero* exposure to environmental oestrogens/anti-androgens results in various symptoms of TDS.

This research project aim was only to indicate potential explanatory factors and in order to fully assess associations between possible factors and these disease/conditions further studies are required.

Further studies are required that look at the overall burden of male reproductive health disease i.e. all conditions based on good quality data. This research project appears to be the first of its kind to assess several indicators of male reproductive health jointly, but more are required to fully explore potential explanatory factors and the common aetiology of these disease/conditions.

Although there appears to be studies that attempt to estimate semen quality on a representative sample of the population, more are required. These studies would not only provide an estimate of semen quality that would overcome some of the limitations of previous work but provide an estimate of a current birth cohort. This cohort could then be compared with another cohort selected in the future so as to assess if there are temporal trends in semen quality. Furthermore, these population studies could be used to explore possible aetiology of semen quality and give a consensus on conclusions based on data where some of the limitations of previous work have been minimised.

As mentioned earlier there might be under-reporting of cryptorchidism and hypospadias in these datasets as cases have not been identified at birth. The need for high quality, consistently collected data on congenital anomalies is one that would not only assist in future work on male reproductive health but other aspects of epidemiology. While logistically this is not straightforward, developments of national congenital registers is currently underway at ISD.

Although not highlighted by this research project the final suggestion for future research on male reproductive health stems from the assessment of current research and is a key issue. Further work is required to explain and describe the biological mechanisms between environmental oestrogens and/or anti-androgens and the anomalies of male reproductive health. In particular, to show the relationship



between *in utero* exposure to oestrogens and/or anti-androgens and the male reproductive health anomalies. One possible study would be to assess the foetal environment and follow up for the subsequent outcomes. The ethical and practical obstacles to this type of study would be substantial. However, there is a potential source for these data. The Avon Longitudinal Study of Parents and Children (ALSPAC – [www.alspac.bris.ac.uk](http://www.alspac.bris.ac.uk)) is a birth cohort study that has data both from children and parents. This source of data would potentially include all elements that might be associated with the conditions and so fully assess the possibly multifaceted aetiology. Until research is carried that looks at all the potential pathways and mechanisms to these conditions of male reproductive health then the TDS hypothesis will remain just that, a hypothesis.

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**Appendix 1 File format of hypospadias and cryptorchidism dataset**

Description	Notes
Year and month of birth of baby	
Postcode Sector of mother relating to baby	99999 = missing postcode sector
Hospital code	
Number of births	
Birth order	
Estimated gestation	
Diagnosis Code of Interest 1	ICD9/10 coding dependent on date of birth
Diagnosis Code of Interest 2	ICD9/10 coding dependent on date of birth
Diagnosis Code of Interest 3	ICD9/10 coding dependent on date of birth
Year and month of birth of mother	
Sex of baby 1	0=Not Known, 1=Male, 2=Female, 8=Other or not known, 9=Not specified
Sex of baby 2	As baby 1
Sex of baby 3	As baby 1 – not on records prior to April 1997
Certainty of gestation	0=Not Applicable, 1=Certain 2=Uncertain, 9=Not known
Smoker during pregnancy	0=No, 1=Yes, 9=Not known This field is not mandatory
	From 1981
	1= Home with mother
	2=Home with mother
	3=To care of relative
	4=Transfer to other ward or hospital (medical)
	5= Transfer to other ward or hospital (surgery)
	6= Residential or foster care
	7=Dead
	9=Other
	9=Not Known
	From 1982
	1=Home with mother
	2=Home after mother
	3=To care of relative
	4=To other ward or hospital (medical or surgery)
	5=To residential/foster care
	6=Dead
	8=Other
	9=Not known
Condition on discharge	From 1992 This file is missing on SMR (EP) records
	1=Home with mother
	2=Home after mother
	3=To relative
	4=To foster care
	5=To other hosp with mother
	6=To other hosp without mother
	8=Other
	9=Not known
	From April 1996
	10=Regular discharge
	11=Discharge from NHS Care
	12=Transfer within the same provide unit
	13=Transfer to another provide unit
	18=Other type pf regular discharge
	40=Death no additional detail
	41= Death (PM)

**Appendix 2    File format of testicular cancer dataset**

Description	Notes
Year and month of birth of baby	
Cancer Incidence date	Full date
Cancer Diagnostic Code	As detailed in 3.4.2
Morphology (histology) of the tumour	First 4 digits of the ICD-0 or ICD-0(2) morphology code dependent on if ICD9 or ICD10 diagnostic code
Hospital or GP of diagnosis	Prior 1997 this field only contain hospital codes
Postcode sector of registration	
Deprivation category (5) – 1991 Census	Via Postcode at registration 1 = least deprived, 5 = most deprived, 9 = not known
Deprivation category (7) – 1991 Census	Via Postcode at registration 1 = least deprived, 7 = most deprived, 9 = not known
Deprivation category (5) – 1981 Census	Via Postcode at registration 1 = least deprived, 5 = most deprived, 9 = not known
Deprivation category (7) – 1981 Census	Via Postcode at registration 1 = least deprived, 7 = most deprived, 9 = not known
Year and month date of Death	From linked death records (only available from 1981)